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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34197 A2

(51) International Patent Classification[7]: A61K 41/00

(21) International Application Number: PCT/US00/30839

(22) International Filing Date: 9 November 2000 (09.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/164,704 11 November 1999 (11.11.1999) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/34197 A2

(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: A method of treating cancer with radiation, in conjunction with the administration of a leukotriene (LTB4) antagonist is disclosed.

ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from United States Provisional Patent Application No. 60/164,704 filed 11 November 1999; the entire disclosure of which is incorporated by reference.

FIELD OF THE INVENTION

This invention relates to a method of treating cancer with radiation therapy. More specifically, it relates to the use of radiation therapy, in conjunction with leukotriene inhibitors that enhance the effectiveness of the radiation therapy.

BACKGROUND OF THE INVENTION

Leukotriene B4 (LTB_4) is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, and shock.

U.S. Patent 5,543,428 discloses the role of leukotriene inhibitors and reversing multi-drug resistance in a multi-drug resistant tumors. U.S. Patent 5,910,505 discloses that leukotriene LTB_4 antagonists may be used for the treatment or inhibition of oral squamous cell carcinoma.

These leukotriene inhibitors are well known in the art, and are fully described in U.S. Patent 5,462,954, which is

hereby specifically incorporated by reference for its disclosure of leukotriene inhibitors, the methods of preparation of specific leukotriene inhibitors, and compounds or formulations of the leukotriene inhibitors which may be administered to patients.

Radiation therapy is commonly used to treat cancers such as prostate cancer and colon cancer. Breast Carcinoma, Bladder Carcinoma, Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Non- Small Cell Lung Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, Pediatric Malignancies and the like.

Several types of radiation are used in the treatment of cancer including X-rays gamma rays, high energy electrons and high LET (Linear Energy Transfer) radiation, such as, protons, neutron, and alpha particles. The ionizing radiation is employed by techniques well known to those skilled in the art. For example, X-rays and gamma rays are applied by external and/or interstitial means from linear accelerators or radioactive sources. High-energy electrons can be produced by linear accelerators and high LET radiation is also applied from radioactive sources implanted interstitially. The total dose of radiation employed by one skilled in the art ranges from 18 to 160 Gray (Gy). (One Gray unit of measure is equal to 100 rads) This total dose of radiation is usually or frequently divided into 5 to 7 continuous weeks of therapy. Typically, one week of

radiation is divided into 5 daily fractions. A daily fraction of radiation consists of a dose from 1.2 to 2.5 Gray. The total amount of radiation used in brachytherapy may be 160 Gy. The exact dosage of radiation is dependent on a variety of factors including but not limited to the volume of the cancerous tissue to be irradiated, normal tissue surrounding the cancerous tissue, age of the patient, medical history of the patient, and other clinical factors. For relevant references, see: R. Arriagada, Hematology/Oncology Clinics of North America, Vol. 11, pgs. 461-472 (1997) and S. Hellman, Principles of Cancer Management: Radiation Therapy, *in* Cancer: Principles and Practice of Oncology, 5th Ed., Lippincott Publishers, pgs. 307-332 (1997); the disclosure of which is herein incorporated by reference.

Whatever the type of radiation used, it is believed that all radiation acts against cancer by a similar mechanism. Cancer cells are dividing rapidly, and it is thought that radiation disrupts the DNA of the cancer cells. This creates problems with cell division, and eventually results in the death of the irradiated cancer cells. Radiation also affects the normal tissue, and can lead to the death of normal cells as well. Accordingly, it is highly desirable to minimize the dose of radiation, to which the patient is exposed, in order to provide a treatment which is effective against cancer cells, and at the same time does not cause excessive damage to normal tissues.

Oxygen can act as a potentiator of radiation. Many tumors have rather low levels of oxygen in the interior of the tumor. Often radiation is more effective if oxygen can

be provided to the tumor cell. Other potentiators are hypoxic cell sensitizers, non-hypoxic cell sensitizers, and oxygen delivery agents. These potentiators produce enhancement ratios between 1 and 3. Certain oxygen delivery agents are taught in US patent 5,295,944.

SUMMARY OF THE INVENTION

Substituted phenylphenol leukotriene (LTB_4) antagonists enhance the effectiveness of radiation therapy in the treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions:

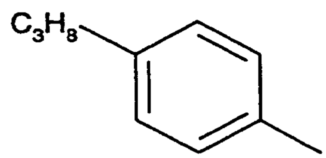
The term, "Acidic Group" means an organic group which when attached as the "Z" substituent of formula (I) or the "Z2" substituent of formula (II) acts as a proton donor capable of hydrogen bonding. An illustrative acidic group is carboxyl.

The term, "Active Ingredient" refers to leukotriene B4 antagonist compounds generically described by formula A as well as diphenyl leukotriene B_4 antagonist compounds generically described by formula I and formula II or the list of specific diphenyl compounds disclosed, infra., and the salts, solvates, and prodrugs of such compounds.

The term, "alkenyl" means a monovalent radical of the generic formula C_nH_{2n} such as ethenyl, n-propenyl, isopropeneyl, n-butenyl, isobutenyl, 2-butenyl, and 3-butenyl.

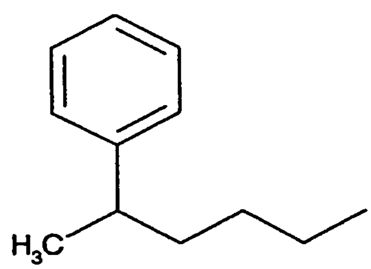
The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkaryl" means an aryl radical substituted with an alkyl or substituted aryl group, for example:



In the term, "C_6-C_{20} alkaryl" the numerical subscripts refer to the total number of carbon atoms in the radical.

The term, "C_6-C_{20} aralkyl" means an alkyl radical substituted with an aryl or substituted aryl group, for example:



In the term, "C_6-C_{20} aralkyl" the numerical subscripts refer to the total number of carbon atoms in the radical.

The term, "carbocyclic group" refers to a five, six, seven, or eight membered saturated, unsaturated or aromatic ring containing only carbon and hydrogen (e.g., benzene, cyclohexene, cyclohexane, cyclopentane).

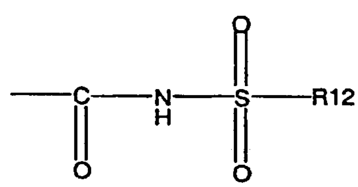
The term, "cycloalkyl" means a carbocyclic non-aromatic monovalent radical such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term, "halo" means fluoro, chloro, bromo, or iodo.

The term, "heterocyclic radical(s)" refers to a radical having a saturated, unsaturated or aromatic five membered substituted or unsubstituted ring containing from 1 to 4 hetero atoms.

The terms, "mammal" and "mammalian" include human.

The term, "N-sulfonamidyl" means the radical:



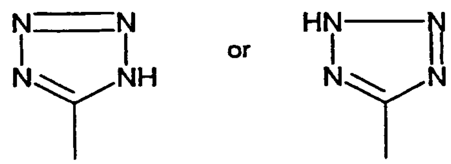
where R12 is C_1-C_{10} alkyl, aryl, C1-C6 alkyl substituted aryl, C_6-C_{20} alkaryl, or C_6-C_{20} aralkyl.

The term, "substituted alkyl" means an alkyl group further substituted with one or more radical(s) selected from halo, C_1-C_6 alkyl, aryl, benzyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_6 haloalkyl (e.g., $-CF_3$).

The term, "substituted aryl" means an aryl group further substituted with one or more radical(s) selected from halo, C_1-C_6 alkyl, aryl, benzyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_6 haloalkyl (e.g., $-CF_3$).

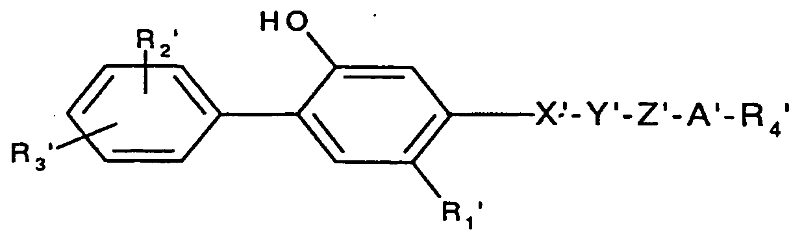
The term, "tetrazolyl" refers to an acidic group represented by either of the formulae:



The term "therapeutically effective interval" is a period of time beginning when one of either (a) radiation treatment or (b) the LTB4 antagonist is administered to a mammal and ending at the limit of the anti-cancer beneficial effect in treating cancer of (a) or (b).

The phrase "therapeutically effective combination", used in the practice of this invention, means administration of both (a) the radiation treatment and (b) the LTB4 antagonist, either simultaneously or separately.

Surprisingly, we have now found a method of treating a human patient suffering from cancer which comprises administering to said patient ionizing radiation in conjunction with an effective amount of a leukotriene (LTB_4) inhibitor. The leukotriene (LTB_4) inhibitors, useful in the present invention, include the compounds of Formula A or a pharmaceutically acceptable base addition salt thereof, wherein:



Formula A

R_1' is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

R_2' and R_3' are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-$S(O)_{\bar{q}}$, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

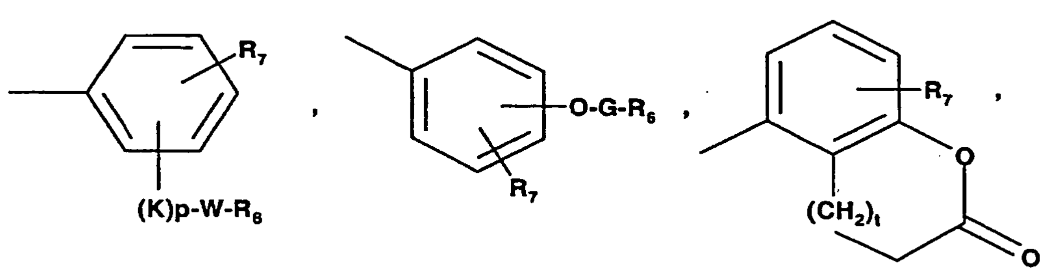
X' is -O-, -S-, -C(=O), or $-CH_2-$;

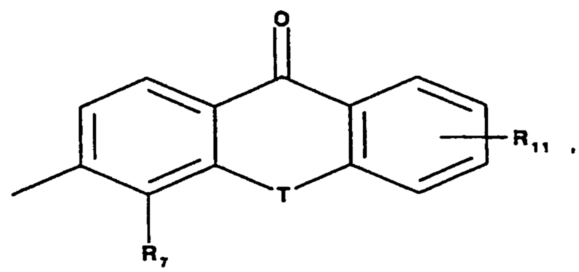
Y' is -O- or $-CH_2-$;

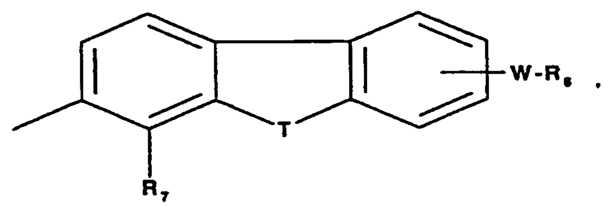
or when taken together, -X-Y- is -CH=CH- or -C≡C-;

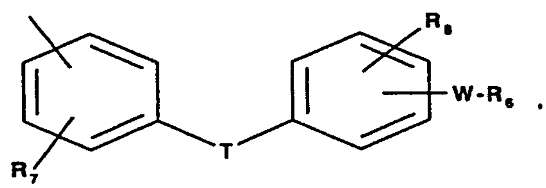
Z' is a straight or branched chain C_1-C_{10} alkylidenyl;

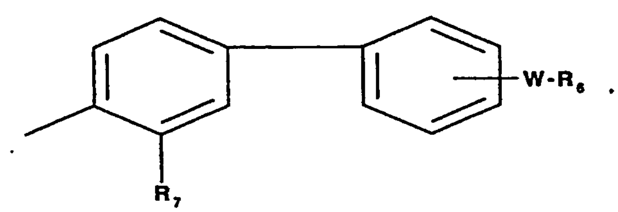
A' is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;











where

each R_6 is independently -COOH, 5-tetrazolyl, -$CON(R_9)_2$, or -$CONHSO_2R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, -W-R_6, -T-G-R_6, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, $-W-R_6$, or $-T-G-R_6$;

each W is a bond or a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $-S(O)_{\overline{q}}$;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

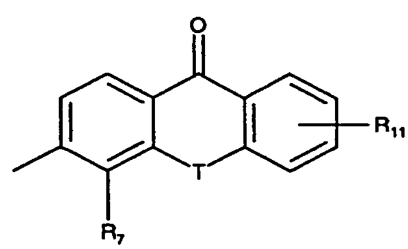
t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

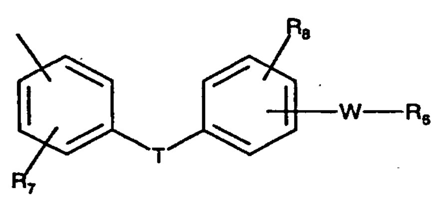
provided when A is -O- or -S-, R_4 is not R_6;

and provided W is not a bond when p is 0.

More preferred compounds of Formula A are those wherein R4' is selected from the following formulae:

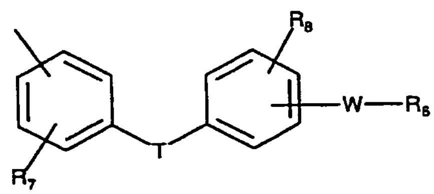


, or



.

An even more preferred compound is that wherein R4'is:



Preferred compounds or pharmaceutically acceptable acid or salt derivatives thereof are those wherein said compound is selected from the group (A) to (KKKK) consisting of:

A) 2-Methyl-2-(1H-tetrazol-5-yl)-7-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)heptane;

B) 2-Methyl-2-(1H-tetrazol-5-yl)-7-(2-ethyl-4-(3-fluorophenyl)-5-hydroxyphenoxy)heptane;

C) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-dimethylaminocarbonylbutyloxy)phenyl) propionic acid;

D) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

E) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxybutyloxy)phenyl)propionic acid;

F) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-methoxyphenyl)propionic acid;

G) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-(1H-tetrazol-5-yl)butyloxy)phenyl)propionic acid;

H) Methyl 3-(2-(4-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)-(1-butenyl))phenyl)propionate;

I) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)-(1-butenyl))phenyl)propionic acid;

J) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyl)phenyl)propionic acid;

K) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyl)-6-methoxyphenyl)propionic acid;

L) Methyl 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-hydroxyphenyl)propionate;

M) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-hydroxyphenyl)propionic acid;

N) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-butyloxy)phenyl)propionic acid;

O) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-methylthiobutyloxy)phenyl)propionic acid;

P) 3-(2-(3-(2,4-Di-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxybutoxy)phenyl)propionic acid;

Q) 6-Methyl-6-(1H-tetrazol-5-yl)-11-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)undecane;

R) N,N-Dimethyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

S) N-Methanesulfonyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

T) N-Phenylsulfonyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy) propoxy)phenyl)propionamide;

U) 3-(2-(3-(2-Butyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

V) Ethyl 3-(2-(4-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyloxy)phenyl)propionate;

W) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyloxy)phenyl)propionic acid;

X) Methyl 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-(methoxycarbonyl)phenoxy)phenyl)propionate;

Y) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propionic acid;

Z) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-4-(4-carboxyphenoxy)phenyl)propionic acid;

AA) 3,3-Dimethyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

BB) 2-Methyl-2-(1H-tetrazol-5-yl)-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propane;

CC) 2-Methyl-2-(1H-tetrazol-5-yl)-3-hydroxy-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propane;

DD) 3-(2-(3-(2-Bromo-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

EE) 3-(2-(3-(2-Ethylthio-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

FF) Methyl 3-(2-hydroxy-3-(4-methoxycarbonylbutyl)-6-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionate;

GG) 5-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-8-(4-carboxybutyl)dihydrocoumarin;

HH) 2-Phenyl-4-ethyl-5-[6-(2H-tetrazol-5-yl)-6-methylheptyloxy]phenol sodium salt;

II) 2-(4-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

JJ) 2-(3-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

KK) 2-(2-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

LL) 2-(4-Methoxyphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

MM) 2-(3-Methoxyphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

NN) 2-(4-Trifluoromethylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

OO) 2-(3-Dimethylaminophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

PP) 3-(5-(6-(4-Phenyl-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-1,2,3,4 -tetrahydronaphthalen-1(2H)-one)propanoic acid;

QQ) 3-(5-(6-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymeth yl-1,2,3,4-tetrahydronaphthalen-1(2H)-one)propanoic acid;

RR) 3-(4-(5-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-2,3-dihydroinden-1(2H)-one)propanoic acid;

SS) 3,3-Dimethyl-5-(3-(2-carboxyethyl)-4-(3-(4-fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)phenyl)-5-oxopentanoic acid;

TT) 7-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

UU) 8-Propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

VV) 2-[3-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]propanoic acid;

WW) 2-(4-Chlorophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol monosodium salt;

XX) 2-(3,5-Dichlorophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol monosodium salt;

YY) 3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt;

ZZ) 7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate;

AAA) 2-[2-Propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid sodium salt hemihydrate;

BBB) 3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy][1,1'-biphenyl]-4-propanoic acid disodium salt monohydrate;

CCC) 5-Ethyl-4-[3-[2-propyl-3-[2-(2H-tetrazol-5-yl)phenoxy]phenoxy]propoxy][1,1'-biphenyl]-2-ol disodium salt sesquihydrate;

DDD) 3-[4-[3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9-oxo-9H-xanthene]]propanoic acid sodium salt hemihydrate;

EEE) 2-Fluoro-6-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid disodium salt;

FFF) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt;

GGG) 3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]] propanoic acid disodium salt trihydrate;

HHH) 3-[4-[9-Oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid;

III) 3-[2-[1-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-4-(5-oxo-5-morpholinopentanamido)phenyl]propanoic acid;

JJJ) 2-Fluoro-6-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid disodium salt hydrate;

KKK) 4-Fluoro-2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

LLL) 2-[2-Propyl-3-[5-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]pentoxy]phenoxy]benzoic acid;

MMM) 2-[2-Propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]butoxy]phenoxy]benzoic acid sesquihydrate;

NNN) 2-[2-(2-Methylpropyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

OOO) 2-[2-Butyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid hydrate;

PPP) 2-[2-(Phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

QQQ) 2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]phenylacetic acid;

RRR) 2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid;

SSS) 2-[[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl] benzoic acid;

TTT) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid;

UUU) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfinyl] benzoic acid;

VVV) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfonyl] benzoic acid hydrate;

WWW) 5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]-4-pentynoic acid disodium salt 0.4 hydrate;

XXX) 1-Phenyl-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

YYY) 1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

ZZZ) 1-(4-(Dimethylaminocarbonylmethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

AAAA) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)-E-propenoic acid;

BBBB) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)-2-methyl-E-propenoic acid;

CCCC) 5-(2-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)ethyl)-1H-tetrazole;

DDDD) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-4-(4-carboxybutyloxy)phenyl)propionic acid;

EEEE) 5-[3-[4-(4-Fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-one;

FFFF) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}phenyl)propanoic acid;

GGGG) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-4-propylphenyl)propanoic acid sodium salt;

HHHH) 3-(4-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-3-propylphenyl)propanoic acid;

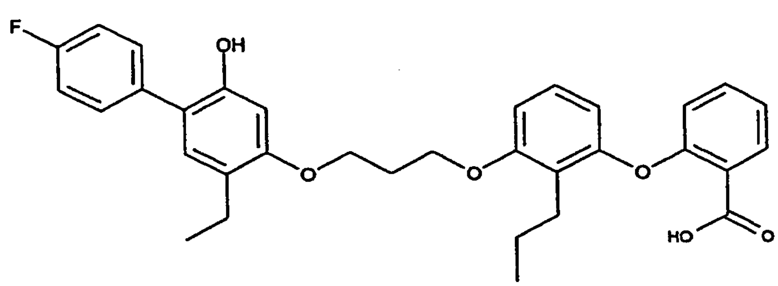
IIII) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-2-propylphenyl)propanoic acid;

JJJJ) 3-{3-[3-(2-Ethyl-5-hydroxyphenyloxy)propoxy]-2-propylphenyl}propanoic acid disodium salt; and

KKKK) 2-[3-[3-[2-Ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid disodium salt hemihydrate.

A most preferred compound is:

2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy] benzoic acid which can also be named 2-[3-[3-(5-ethyl-4'-fluoro-2-hydroxybiphen-4-yloxy)propoxy]-2-propylphenoxy]benzoic acid



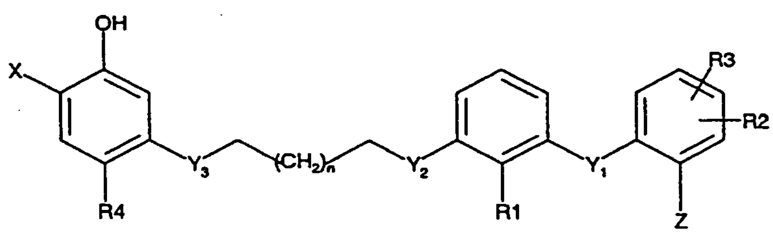
Formula IV

A second class of LTB_4 antagonists to use as the essential co-agent in the compositions and practice of the method of this invention are those disclosed in copending provisional patent application, titled, "Heterocycle Substituted Diphenyl Leukotriene Antagonists" (inventor, Jason Scott Sawyer) containing 97 pages and identified as Eli Lilly and

Company Docket No. B-13240), filed on November 11, 1999, and now Provisional patent Application Serial Number 60/164,786. The subject heterocycle substituted diphenyl leukotriene antagonists are also described in more detail below:

II. Additional LTB4 Antagonists:

Additional LTB4 antagonists are described below which are novel heterocyclic substituted diphenyl compounds of formula (I)



(I)

wherein:

X is selected from the group consisting of,

(i) a five membered substituted or unsubstituted heterocyclic radical containing from 1 to 4 hetero atoms independently selected from sulfur, nitrogen or oxygen; or

(ii) a fused bicyclic radical wherein a carbocyclic group is fused to two adjacent carbon atoms of the five membered heterocyclic radical, (i);

Y_1 is a bond or divalent linking group containing 1 to 9 atoms;

Y_2 and Y_3 are divalent linking groups independently selected from $-CH_2-$, -O-, and -S-;

Z is an Acidic Group;

R1 is C_1-C_{10} alkyl, aryl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6-C_{20} aralkyl, C_6-C_{20} alkaryl, C_1-C_{10} haloalkyl, C_6-C_{20} aryloxy, or C_1-C_{10} alkoxy;

R2 is hydrogen, halogen, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, Acidic Group, or $-(CH_2)_{1-7}$(Acidic Group);

R3 is hydrogen, halogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} aryloxy, C_3-C_8 cycloalkyl;

R4 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl, $-(CH_2)_{1-7}$(cycloalkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, benzyl, or aryl; and

n is 0, 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof.

III. Preferred LTB4 Antagonists include the following:

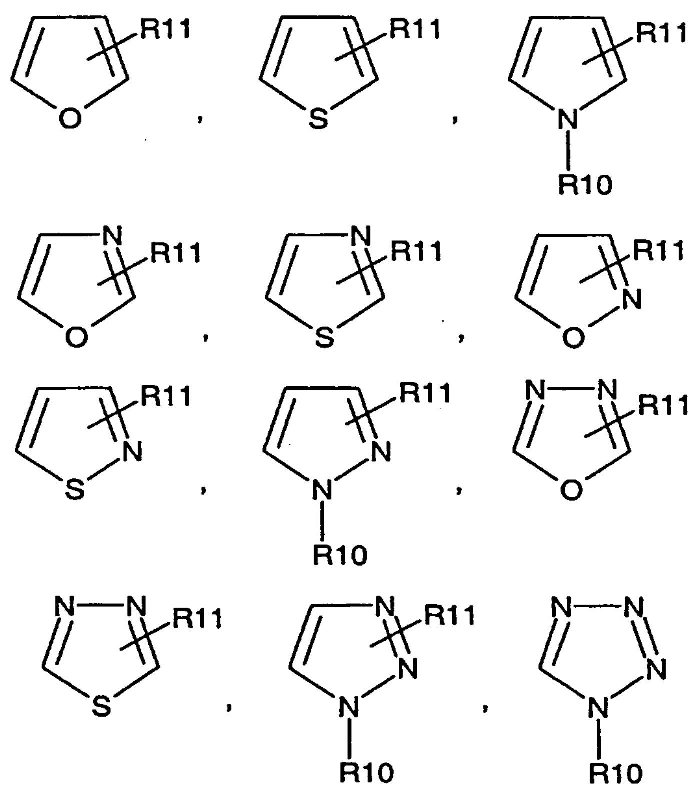
III A. Preferred X substituents:

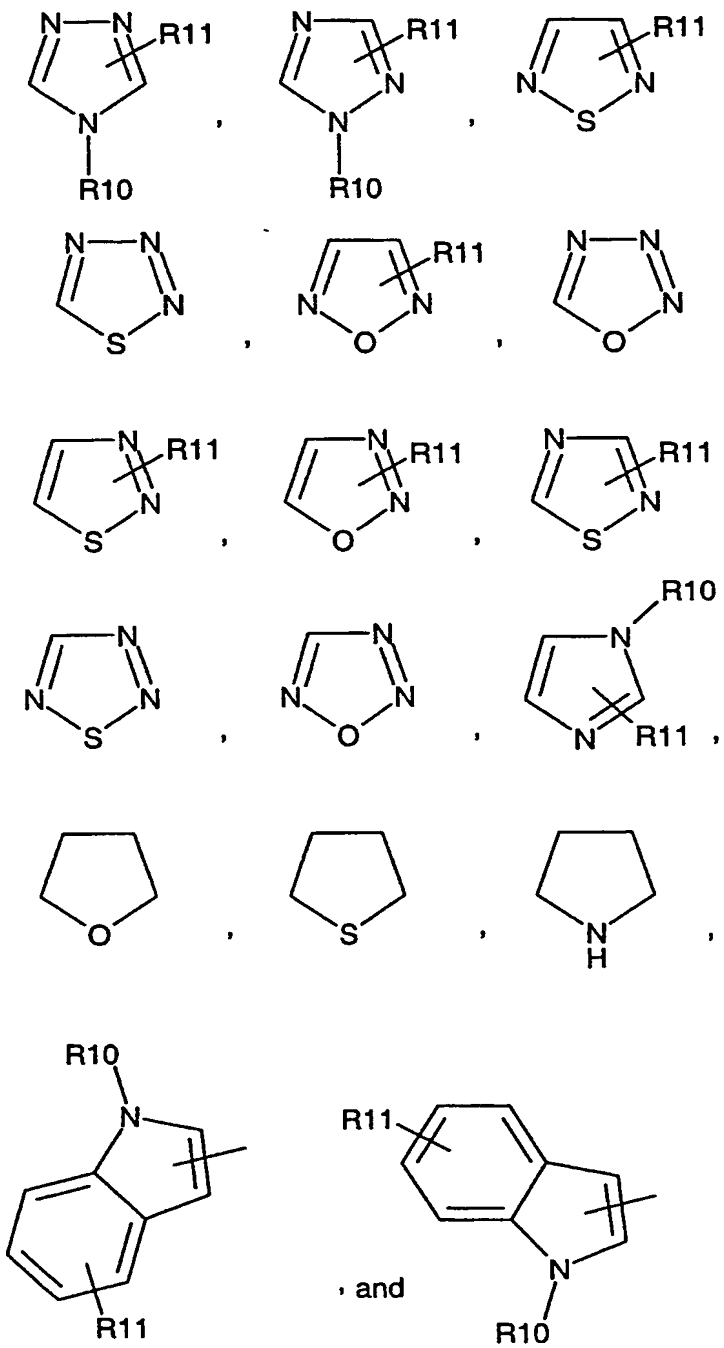
A "substituted heterocyclic radical" is preferably Substituted with from 1 to 3 groups independently selected

from hydrogen, halo, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, aryl, or C_6-C_{20} aryloxy.

Preferred Group 1 of X substituent (symbol, "PG1-X")

Preferred LTB4 compounds of the invention are those wherein X is a heterocyclic radical selected from the group consisting of substituents represented by the following structural formulae:





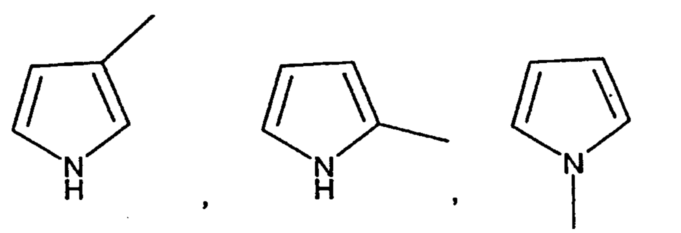
R11
R10
N
S
O
NH
H
and

;

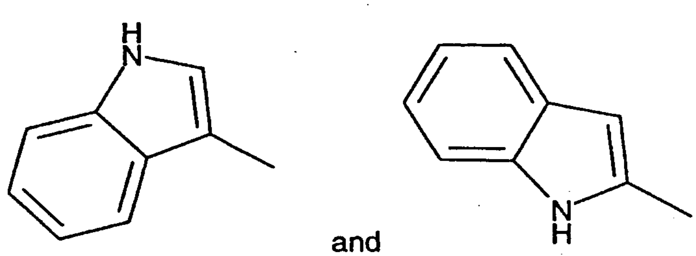
where R10 is a radical selected from hydrogen or C_1-C_4 alkyl; and R11 is a radical selected from hydrogen, halo, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, aryl, or C_6-C_{20} aryloxy. Preferred R10 groups are hydrogen, methyl, or phenyl. Moreover, any of the above heterocyclic radicals illustrated by structural formulae may attach to the diphenyl leukotriene antagonist of formulae (I) by any monovalent bond originating on a suitable carbon or nitrogen atom in its ring structure.

For example, the pyrrole radical may attach to the diphenyl molecule by a single bond originating at any carbon atom or any nitrogen atom which has less than three bonds in the heterocyclic ring;

Location of attachment bond for pyrrole,

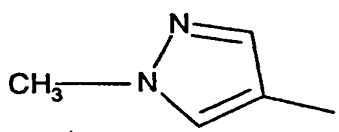
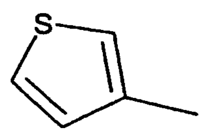
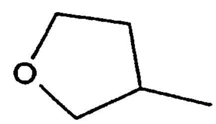


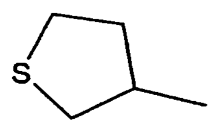
A preferred form of the substituent X is a fused bicyclic radical wherein a carbocyclic group is fused to two adjacent carbon atoms of the five membered heterocyclic radical, for example:



III B. Preferred Group 2 of X substituent (symbol, "PG2-X"):

Most preferred as the X substituents are the heterocyclic radicals;


, 
, 
, or



III C. Excluded X substituents:

The heterocyclic radical X of Formula (I) does not include 3-bromo-1,2,4 thiadiazole since the LTB_4 antagonist activity of compounds containing this radical is considered too low to be an aspect of this invention.

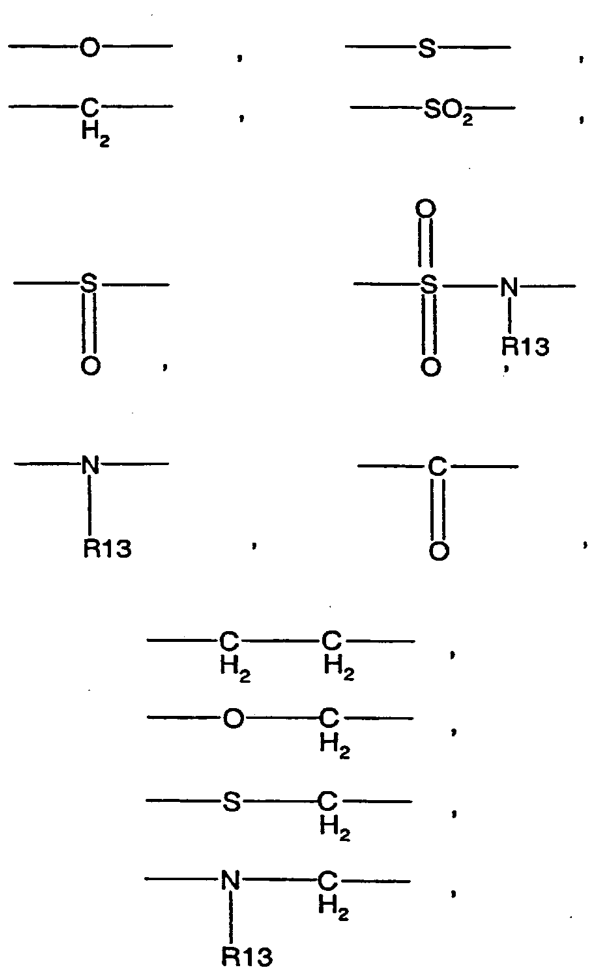
III D. Preferred Y_1 substituents:

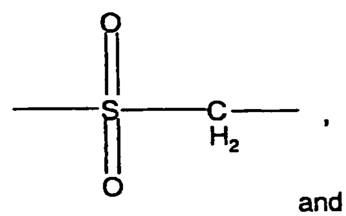
Y_1 is a bond or divalent linking group containing 1 to 9 atoms independently selected from carbon, hydrogen, sulfur, nitrogen, and oxygen;

Preferred Group 1 of Y_1 substituent (symbol, "PG1-Y_1")

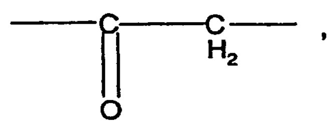
Preferred LTB4 compounds of the invention are those wherein Y_1 is a divalent linking group selected from the

group consisting of substituents represented by the following formulae:



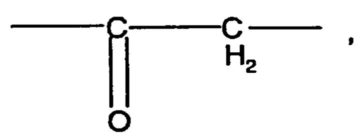


and

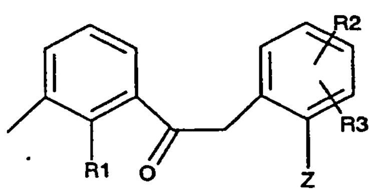


where R13 is hydrogen, methyl, or ethyl;

The above divalent groups may be used in their forward or reversed positions. For example, the group;



may be positioned as either,



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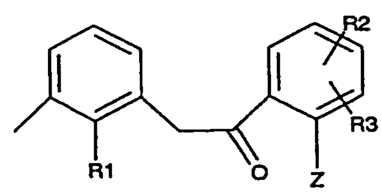


in the displayed fragment of formula (I).

III E. Preferred Group 2 of Y_1 substituent (symbol, "PG2-Y_1"):

The most preferred divalent Y_1 substituent is the group;

—O— .

III F. Preferred Group 1 of Y_2 substituent (symbol, "PG1-Y_2") and Preferred Group 1 of Y_3 substituent (symbol, "PG1-Y_3"):

The Y_2 and Y_3 substituents are preferably selected from -S- and -O-.

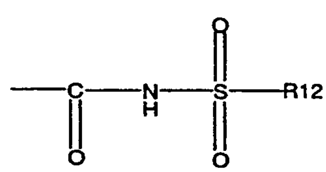
III G. Preferred Group 2 of Y_2 substituent (symbol, "PG2-Y_2") and Preferred Group 2 of Y_3 substituent (symbol, "PG2-Y_3"):

Most preferably both Y_2 and Y_3 are the group;

—O— .

III H. Preferred Group 1 of Z substituent (symbol, "PG1-Z"):

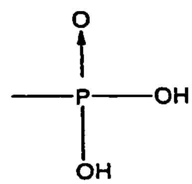
Z is the Acidic Group as previously defined. Preferred is an acidic group selected from the following:



,

tetrazolyl,

$-SO_3H$,



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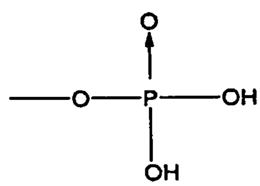

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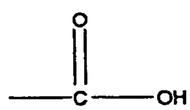

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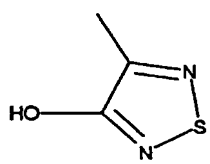
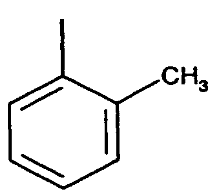


where R12 is C_1-C_{10} alkyl, aryl, C_6-C_{20} alkaryl, or C_6-C_{20} aralkyl. Preferred R12 groups are represented by the formulae:



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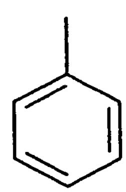


.

III I. Preferred Group 2 of Z substituent (symbol, "PG2-Z"):

Highly preferred are the acidic groups; -5-tetrazolyl,

N-acyl sulfonamide, $-SO_3H$, and carboxyl.

III J. Preferred Group 3 of Z substituent (symbol, "PG3-Z"):

Carboxyl is the most preferred Z substituent.

III K. Preferred Group 1 of n subscript variable (symbol, "PG1-n")

The most preferred integer values for the divalent linking group, $-(CH_2)_n-$, are n=1, n=2, and n=3.

III L. Preferred Group 2 of n subscript variable (symbol, "PG2-n")

The most preferred integer value of n for the divalent linking group, $-(CH_2)_n-$ is n = 1.

III M. Preferred Group 1 of R1 substituent (symbol, "PG1-R1"):

A preferred R1 group is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, and 2-propenyl; with n-propyl being most preferred.

III N. Preferred Group 1 of R2 substituent (symbol, "PG1-R2")and Preferred Group 1 of R3 substituent (symbol, "PG1-R3"):

Preferred R2 and R3 groups are those wherein R2 and R3 are independently selected from hydrogen or methyl, ethyl, methoxy, ethoxy, halo, or $-CF_3$; with R2 and R3 both being hydrogen as most preferred.

III O. Preferred Group 1 of R4 substituent (symbol, "PG1-R4":)

Preferred R4 substituents are ethyl, propyl, and isopropyl.

III P. Combinations of substituents of the compound of Formula (I):

The substituents of formula (I) are defined as "Z", "X", "n", "R1", "R2", "R3", "R4", "Y1", "Y2", and "Y3". Moreover, as described in the preceding section, within each of the defined substituents of Formula (I) are "preferred" and "most preferred" subgroups which define the variety of substituents to be used in the definition of LTB_4 antagonists of the invention. These preferred subgroups are defined by designations such as "PG1-R4" as recited above. It is often advantageous to use combinations of preferred groups or combinations of preferred groups together with the general definition of variables given in Formula (I). Suitable combinations of substituents are shown in the following three Tables (viz., R-Table, Y-Table & XZn-Table).

The following R-Table is used to select combinations of general and preferred groupings of the variables R1, R2, R3 and R4 for substitution in formula (I), as follows:

R-Table

R variables Combination Code	R1 group choice	R2 group choice	R3 group choice	R4 group choice
R01	R1	R2	R3	R4
R02	R1	R2	R3	PG1-R4
R03	R1	R2	PG1-R3	R4
R04	R1	R2	PG1-R3	PG1-R4
R05	R1	PG1-R2	R3	R4
R06	R1	PG1-R2	R3	PG1-R4
R07	R1	PG1-R2	PG1-R3	R4
R08	R1	PG1-R2	PG1-R3	PG1-R4
R09	PG1-R1	R2	R3	R4
R10	PG1-01	R2	R3	PG1-R4
R11	PG1-R1	R2	PG1-R3	R4
R12	PG1-R1	R2	PG1-R3	PG1-R4
R13	PG1-R1	PG1-R2	R3	R4
R14	PG1-R1	PG1-R2	R3	PG1-R4
R15	PG1-R1	PG1-R2	PG1-R3	R4
R16	PG1-R1	PG1-R2	PG1-R3	PG1-R4

Thus, for example, the substituent combination, "R14" describes a substituent combinatorial choice for Formula (I) wherein R1 is selected from the preferred set of variables, "PG1-R1", that is, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, and 2-propenyl; the R2 substituent is selected from the preferred set of

variables, "PG1-R2", that is, hydrogen or methyl, ethyl, methoxy, ethoxy, halo, or $-CF_3$; the variable R3 has the scope defined in the generic formula (I), and the substituents suitable for R4 are selected from the preferred group, "PG1-R4" having the preferred set of variables, ethyl, propyl, and isopropyl.

The following Y-Table is used to select broad and preferred groupings of the variables Y1, Y2, and Y3 for substitution in formula (I), as follows:

Y-Table

Y variables combination code	Y1 group choice	Y2 group choice	Y3 group choice
Y01	Y1	Y2	Y3
Y02	Y1	Y2	PG1-Y3
Y03	Y1	Y2	PG2-Y3
Y04	Y1	PG1-Y2	Y3
Y05	Y1	PG2-Y2	Y3
Y06	Y1	PG1-Y2	PG1-Y3
Y07	Y1	PG1-Y2	PG2-Y3
Y08	Y1	PG2-Y2	PG1-Y3
Y09	Y1	PG2-Y2	PG2-Y3
Y10	PG1-Y1	Y2	Y3
Y11	PG1-Y1	Y2	PG1-Y3
Y12	PG1-Y1	Y2	PG2-Y3
Y13	PG1-Y1	PG1-Y2	Y3
Y14	PG1-Y1	PG1-Y2	PG1-Y3
Y15	PG1-Y1	PG1-Y2	PG2-Y3
Y16	PG1-Y1	PG2-Y2	Y3
Y17	PG1-Y1	PG2-Y2	PG1-Y3
Y18	PG1-Y1	PG2-Y2	PG2-Y3
Y19	PG2-Y1	Y2	Y3
Y20	PG2-Y1	Y2	PG1-Y3
Y21	PG2-Y1	Y2	PG2-Y3
Y22	PG2-Y1	PG1-Y2	Y3
Y23	PG2-Y1	PG1-Y2	PG1-Y3
Y24	PG2-Y1	PG1-Y2	PG2-Y3
Y25	PG2-Y1	PG2-Y2	Y3
Y26	PG2-Y1	PG2-Y2	PG1-Y3
Y27	PG2-Y1	PG2-Y2	PG2-Y3

The following XZn-Table is used to select broad and preferred groupings of the variables X, Z, and n for substitution in formula (I), as follows:

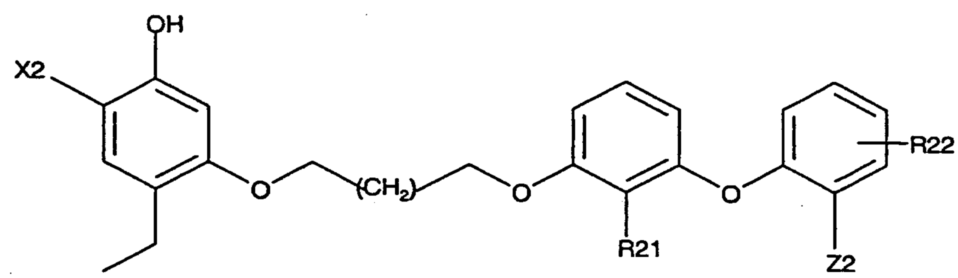
XZn-Table

XZn variables combination code	X group choice	Z Group Choice	n integer group choice
XZn01	X	Z	n
XZn02	X	Z	PG1-n
XZn03	X	Z	PG2-n
XZn04	X	PG1-Z	n
XZn05	X	PG2-Z	n
XZn06	X	PG3-Z	n
XZn07	X	PG1-Z	PG1-n
XZn08	X	PG2-Z	PG1-n
XZn09	X	PG3-Z	PG1-n
XZn10	X	PG1-Z	PG2-n
XZn11	X	PG2-Z	PG2-n
XZn12	X	PG3-Z	PG2-n
XZn13	PG1-X	Z	n
XZn14	PG1-X	Z	PG1-n
XZn15	PG1-X	Z	PG2-n
XZn16	PG1-X	PG1-Z	n
XZn17	PG1-X	PG2-Z	n
XZn18	PG1-X	PG3-Z	n
XZn19	PG2-X	PG1-Z	PG1-n
XZn20	PG2-X	PG2-Z	PG1-n
XZn21	PG2-X	PG3-Z	PG1-n
XZn22	PG2-X	PG1-Z	PG2-n
XZn23	PG2-X	PG2-Z	PG2-n
XZn24	PG2-X	PG3-Z	PG2-n

How to Use the Tables:

Any of the individual 16 combinations of the R substituents depicted in the R-Table may be used in combination with any of the 27 individual combinations of Y substituents depicted in the Y-Table, which may be used with any of the 24 combinations of XZn substituents depicted in the XZn-Table. For example, the substituent combination choice "R07, Y21, XZn03" defines substituent set selections for a subset of formula (I) useful in the practice of the invention.

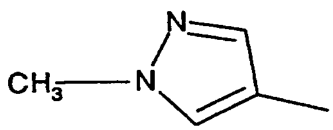
III Q. Additional preferred LTB4 antagonists are described by formula (II):



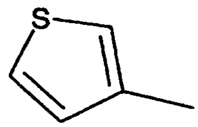
(II)

wherein;

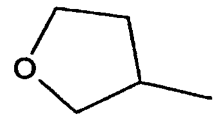
X2 is a heterocyclic radical selected from,



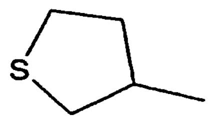
,



,



, or



;

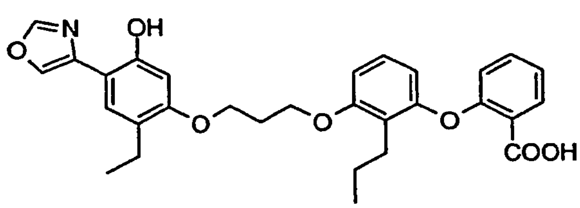
R21 is ethyl, 2-propen-1-yl, 3-propen-1-yl, n-propyl, iso-propyl, n-butyl, sec-butyl, or tert-butyl; and R22 is hydrogen, n-butyl, sec-butyl, fluoro, chloro, $-CF_3$, or tert-butyl.

Z2 is carboxyl, tetrazolyl, N-sulfonamidyl.

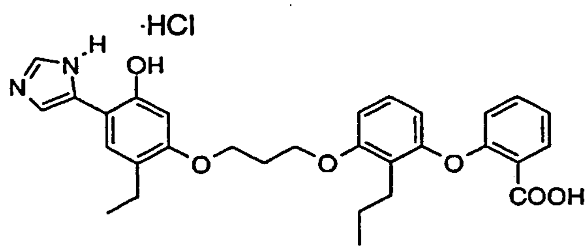
Preferred Compounds of the Invention:

III R. Specific compounds preferred as LTB_4 antagonists are represented by the following structural formulae:

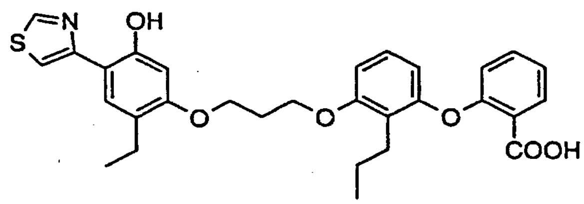
(C1):



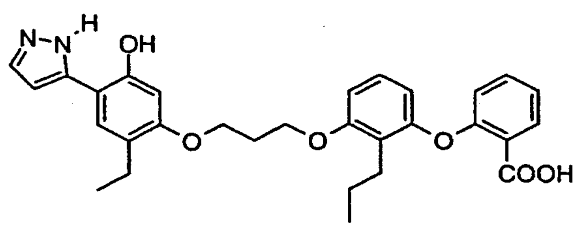
(C2):



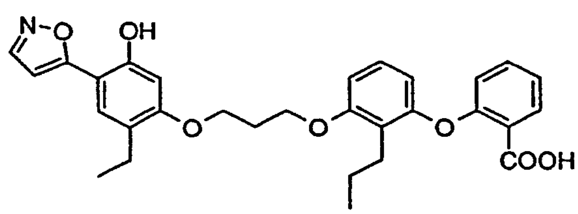
(C3):



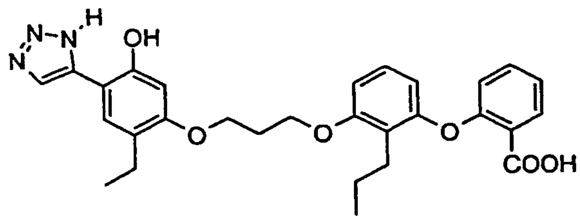
(C4):



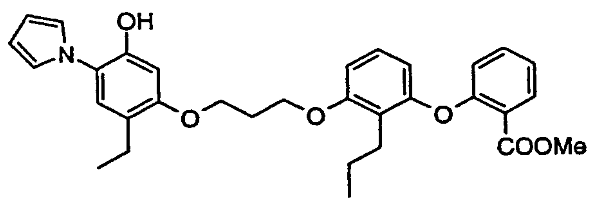
(C5):



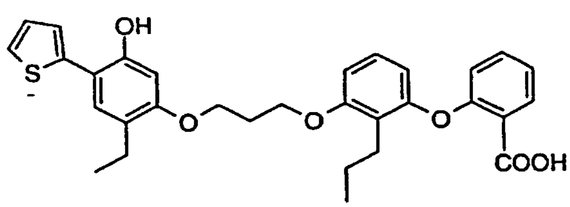
(C6):



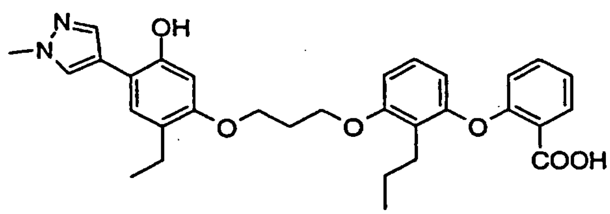
(C7):



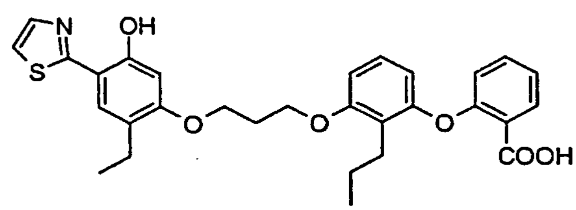
(C8):



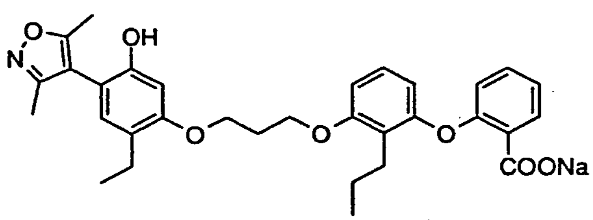
(C9):



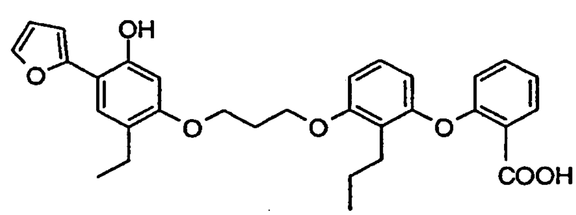
(C10):



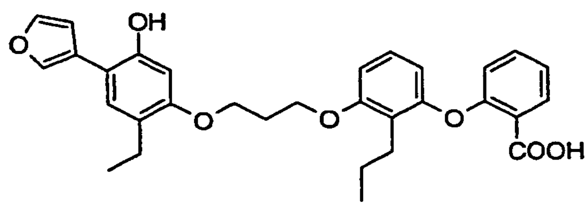
(C11):



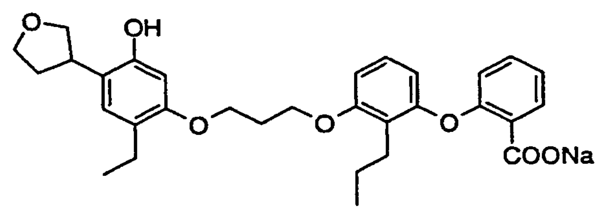
(C12):



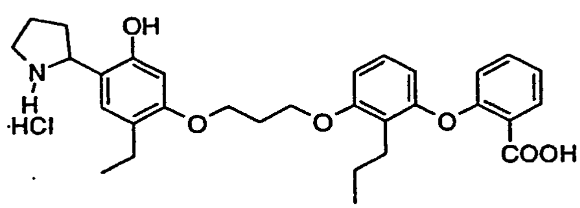
(C13):



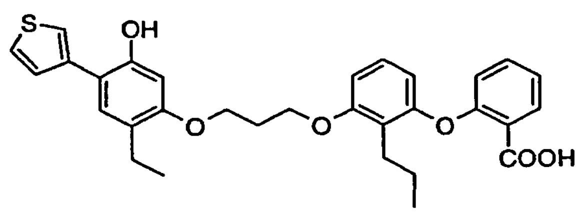
(C14):



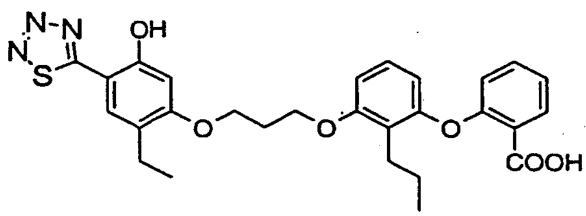
(C15):



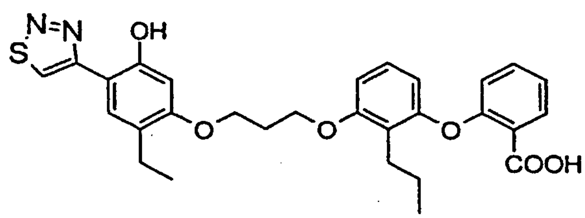
(C16):



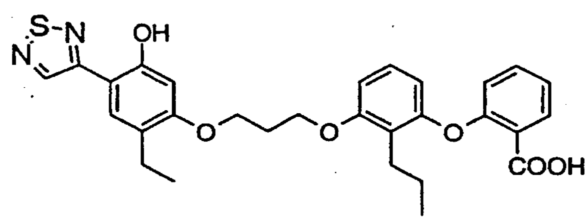
(C17):



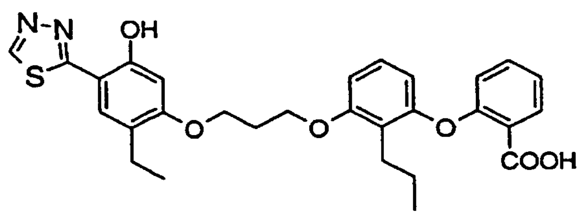
(C18):



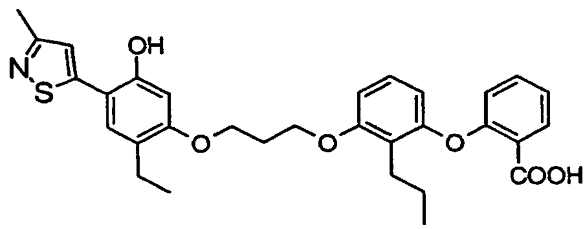
(C19):



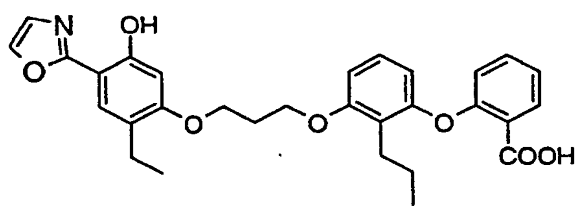
(C20):



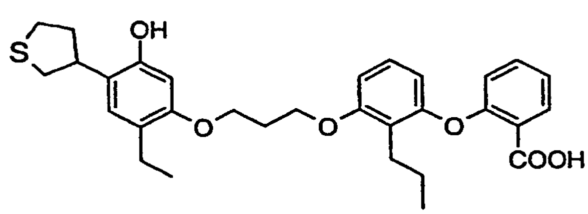
(C21):



(C22):

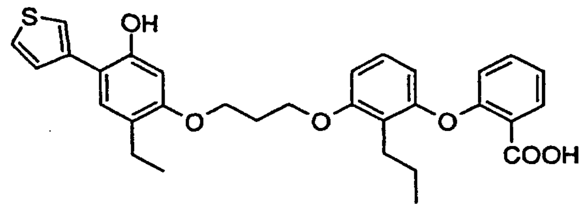


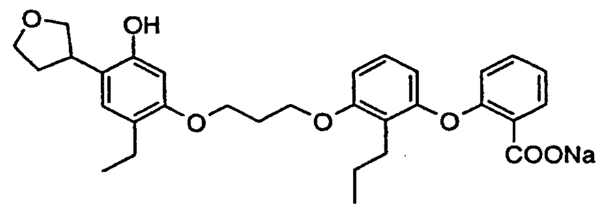
(C23):

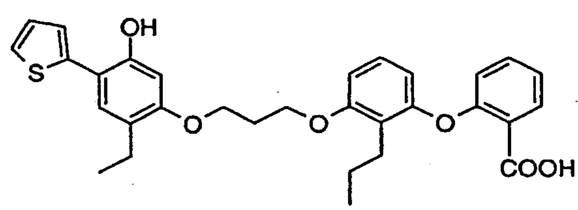


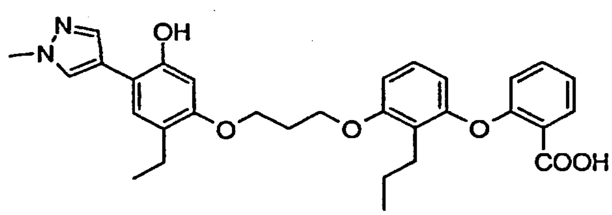
and all acid, salt, solvate and prodrug derivatives thereof.

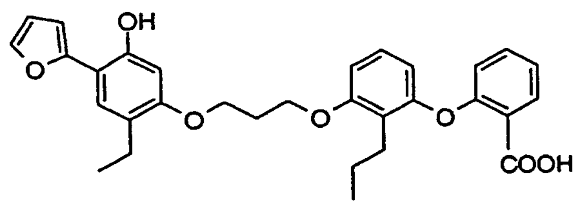
III S. Highly Preferred LTB4 Antagonists are as follows:

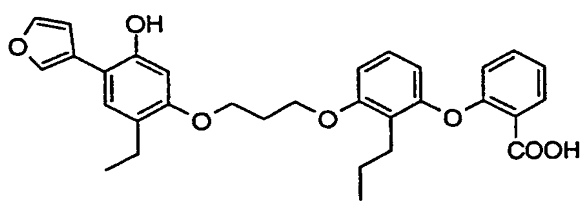












and all acid, salt, solvate and prodrug derivatives thereof.

The salts of the above diphenyl LTB_4 antagonists of the invention, represented by formulae (A),(I) and (II) and the specific compounds set out by structural formulae in sections IIIR and IIIS herein, are an additional aspect of the invention. The compounds of the invention possess an Acidic Group(s) and at these sites various salts may be formed which are more water soluble and/or physiologically suitable than the parent compound in its acid form. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Sodium salts are particularly preferred. Salts are conveniently prepared from the free acid by treating the acid form in solution with a base or by exposing the acid to an ion exchange resin. For example, the (Acidic Group) of the Z of Formula (I) may be selected as $-CO_2H$ and salts may be formed by reaction with

appropriate bases (e.g., NaOH, KOH) to yield the corresponding sodium or potassium salt.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the LTB_4 antagonist compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. All such stereoisomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art, for example, by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively, by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers. Then, because the diastereomers have different melting points, different boiling points, and different solubilities, they can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of Formulae (A), (I) and (II), supra., which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

Esters of carboxylic acids are preferred prodrugs of the compounds of the invention (viz., the compounds of Formula A, Formula I, Formula II and the specific compounds set out in Section IIIR and IIIS, herein).

Methyl ester prodrugs may be prepared by reaction of the acid form of a compound of formula (I) in a medium such as methanol with an acid or base esterification catalyst (e.g., NaOH, H_2SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

Preferred LTB_4 compounds of the invention include the compounds of Formula A, Formula (I), or Formula (II) or the specific compounds of sections IIIR and IIIS shown above by structural formula; wherein the acid, salt and prodrug derivatives thereof are respectively selected from: carboxylic acid, sodium salt, and ester prodrug.

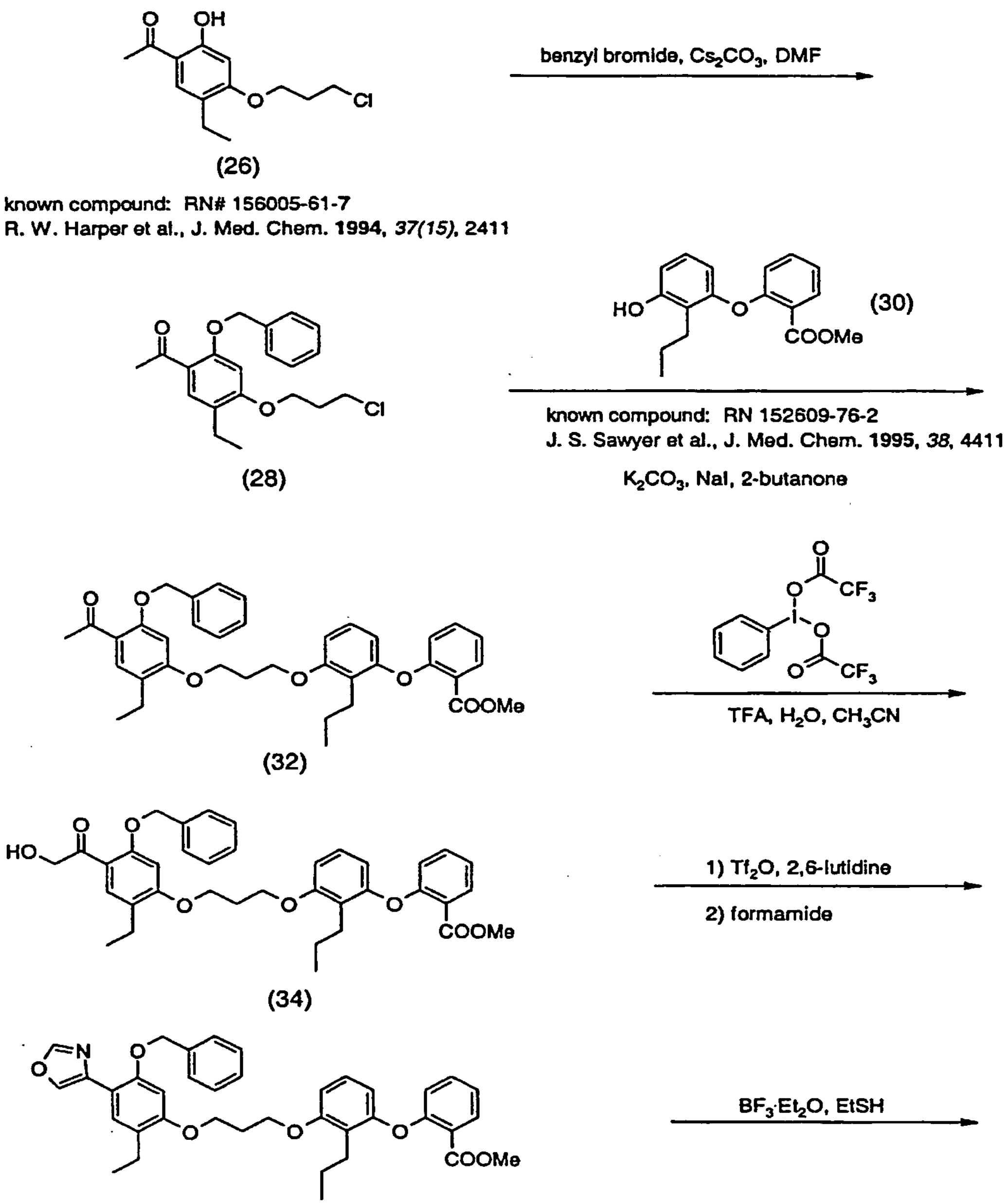
IV. Method of Making the Compounds of the Invention

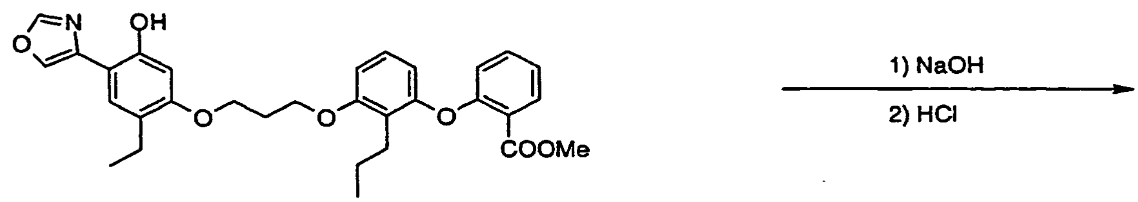
General reaction schemes (not represented to be specific Examples) applicable for synthesis of the LTB_4 antagonist compounds represented by formula (I) are set out below. Numerous literature references and Chemical Abstract registry numbers (e.g., RN 152609-60-4) are supplied as additional aids for preparing reagents used in practicing the synthesis schemes of the invention.

REACTION SCHEMES FOR MAKING THE COMPOUNDS OF THE INVENTION

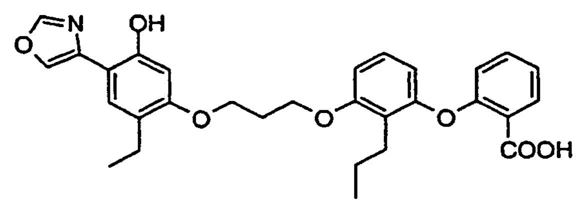
The following scheme illustrates a process for making Example (1), a 4-substituted oxazole LTB_4 receptor antagonist:

Scheme 1


benzyl bromide, Cs_2CO_3, DMF
(26)
known compound: RN# 156005-61-7
R. W. Harper et al., J. Med. Chem. **1994**, *37(15)*, 2411
(30)
known compound: RN 152609-76-2
J. S. Sawyer et al., J. Med. Chem. **1995**, *38*, 4411
K_2CO_3, NaI, 2-butanone
(28)
TFA, H_2O, CH_3CN
(32)
1) Tf_2O, 2,6-lutidine
2) formamide
(34)
$BF_3 \cdot Et_2O$, EtSH
(36)



(38)



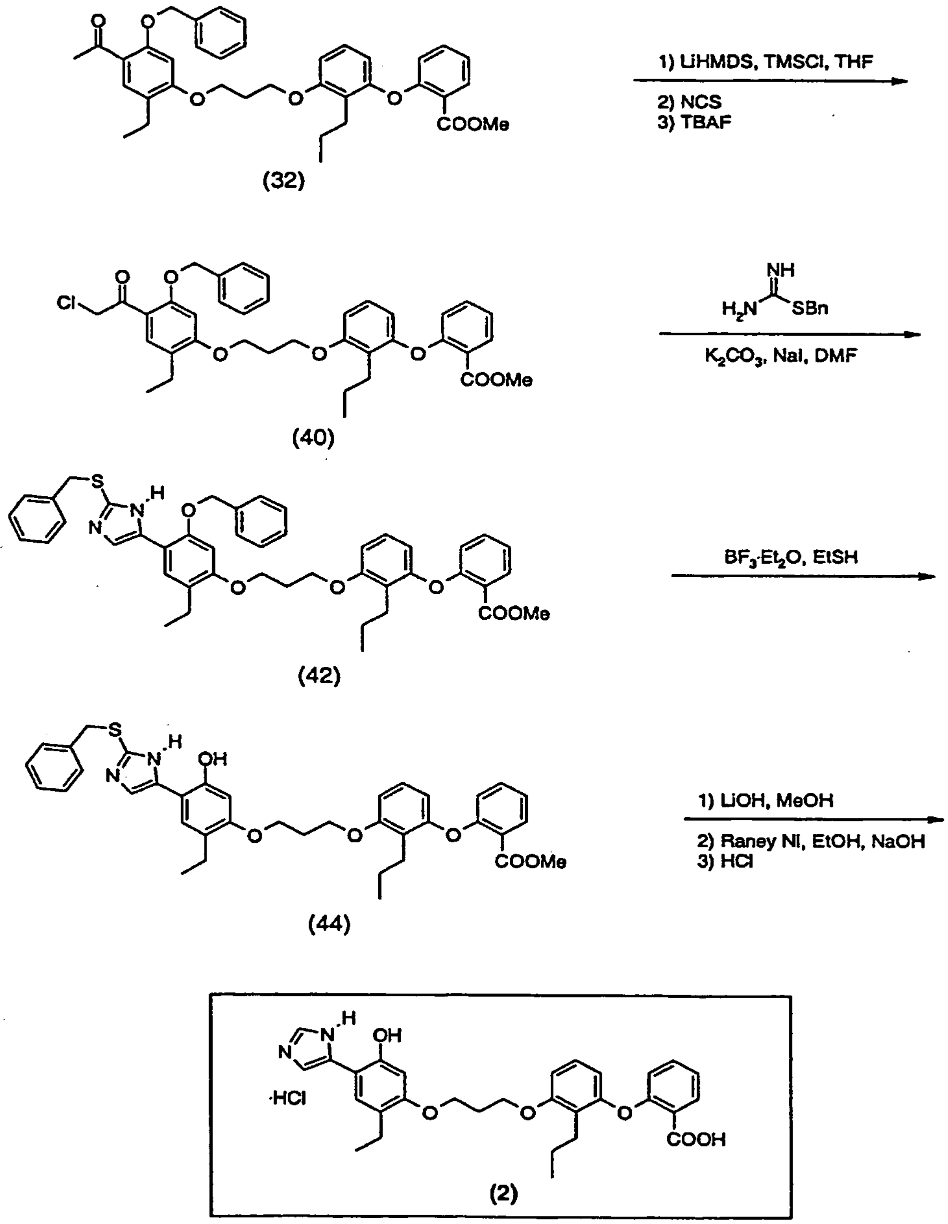
(1)

Known chloride (26) may be alkylated with benzyl bromide to provide chloride (28). Reaction with known ester (30), catalyzed by a suitable base, provides acetophenone (32). Oxidation with bis(trifluoroacetoxy)iodobenzene gives alpha-hydroxy ketone (34), that may be cyclized with triflic anhydride and formamide to give the 4-substituted oxazole (36). Debenzylation with boron trifluoride etherate and ethanethiol gives oxazole (38), that is hydrolyzed and protonated to provide Example (1).

Scheme 2

The following scheme illustrates a process for making Example (2), a 5(4)-substituted imidazole LTB_4 receptor antagonist:

Scheme 2

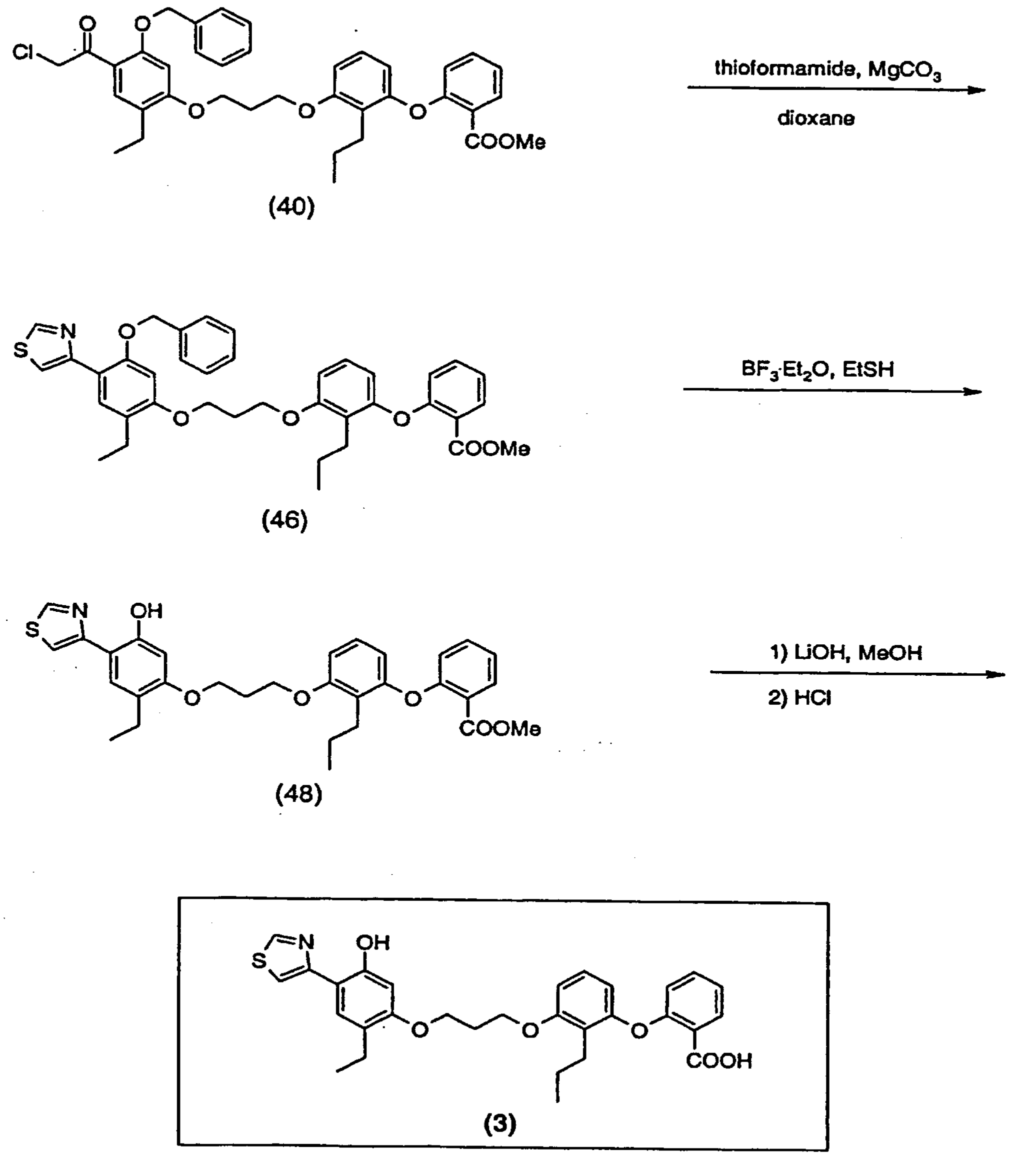

COOMe
(32)
1) LiHMDS, TMSCl, THF
2) NCS
3) TBAF
Cl
COOMe
(40)
NH
H2N SBn
K2CO3, NaI, DMF
S
N
H
COOMe
(42)
BF3·Et2O, EtSH
S
N
H
OH
COOMe
(44)
1) LiOH, MeOH
2) Raney Ni, EtOH, NaOH
3) HCl
N
H
OH
·HCl
COOH
(2)

The trimethylsilyl enol ether of acetophenone (32) is formed and treated with N-chlorosuccinimide followed by tetra-*n*-butylammonium fluoride to provide the chloroketone (40). Treatment of (40) with 2-benzyl-2-thiopseudourea and base provides imidazole (42), that is treated with boron trifluoride etherate and ethanethiol to give imidazole (44). Hydrolysis and protonation provide Example (2) as the hydrochloride salt.

Scheme 3

The following scheme illustrates a process for making Example (3), a 4-substituted thiazole LTB_4 receptor antagonist:

Scheme 3

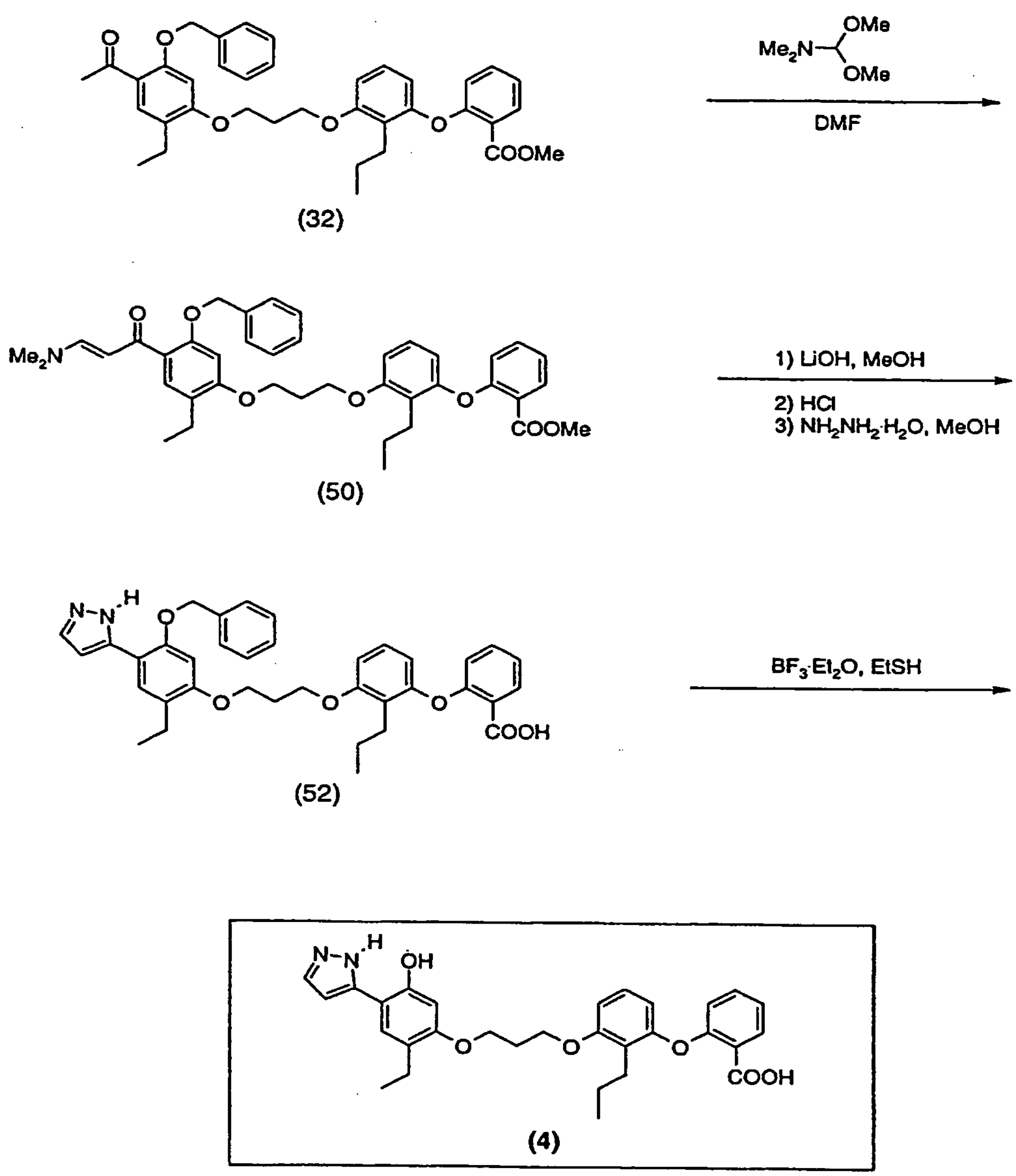

Cl
O
O
COOMe
(40)
thioformamide, MgCO$_3$
dioxane
S
N
(46)
BF$_3$·Et$_2$O, EtSH
OH
(48)
1) LiOH, MeOH
2) HCl
COOH
(3)

Chloroketone (40) is treated with thioformamide and magnesium carbonate to give thiazole (46), that is debenzylated with boron trifluoride etherate and ethanethiol giving thiazole (48). Hydrolysis and protonation provides Example (3).

Scheme 4

The following scheme illustrates a process for making Example (4), a 5(3)-substituted pyrazole LTB_4 receptor antagonist:

Scheme 4

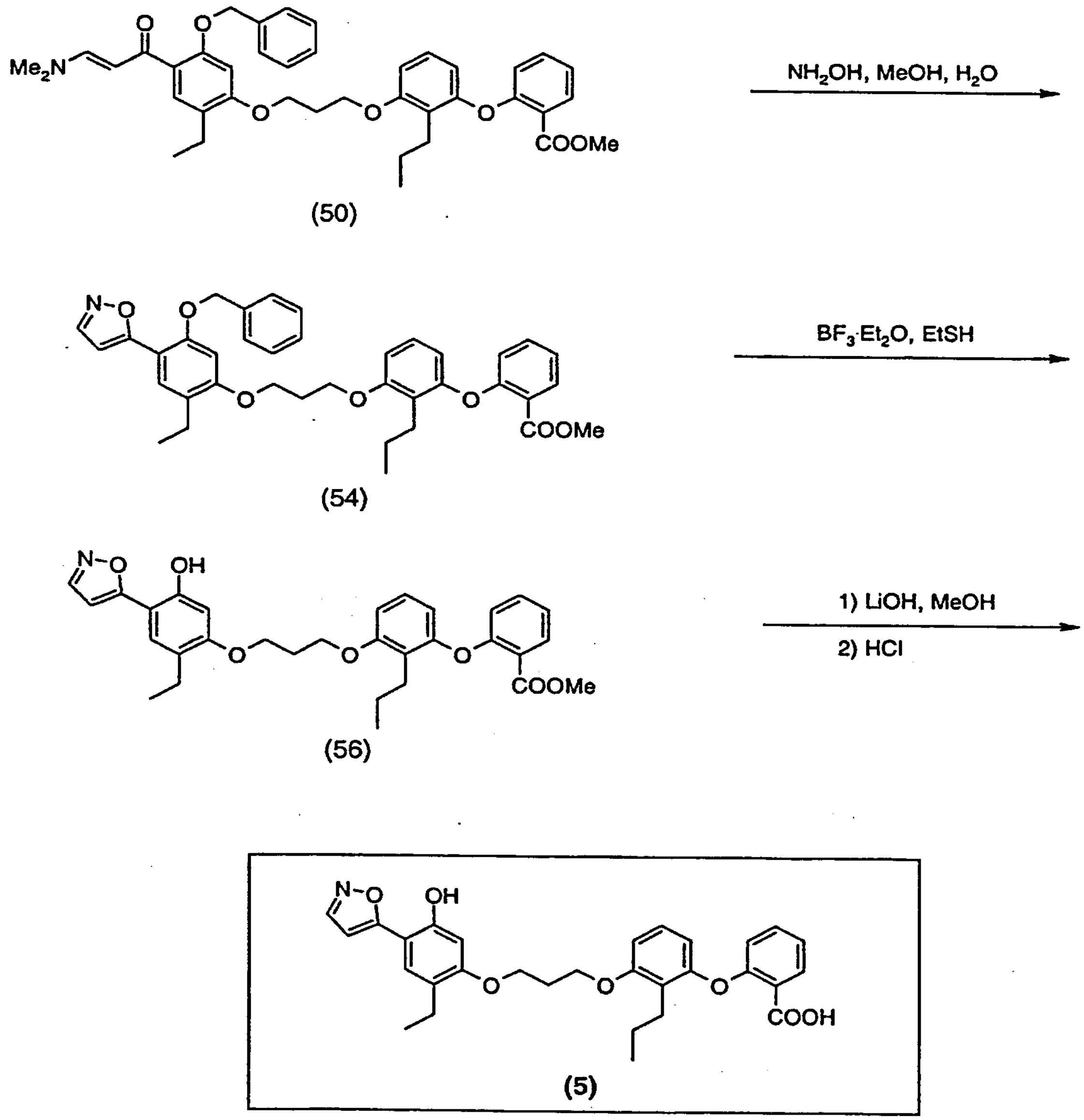

OMe
Me_2N
OMe
DMF
COOMe
(32)
Me_2N
COOMe
(50)
1) LiOH, MeOH
2) HCl
3) $NH_2NH_2{\cdot}H_2O$, MeOH
N-N
H
COOH
(52)
$BF_3{\cdot}Et_2O$, EtSH
N-N
H
OH
COOH
(4)

Treatment of acetophenone (32) with N,N-dimethylformamide dimethyl acetal gives enone (50), that may be hydrolyzed, protonated, and then heated with hydrazine hydrate to provide pyrazole (52). Debenzylation of the resulting pyrazole with boron trifluoride etherate and ethanethiol gives Example (4).

Scheme 5

The following scheme illustrates a process for making Example (5), a 5-substituted isoxazole LTB_4 receptor antagonist:

Scheme 5

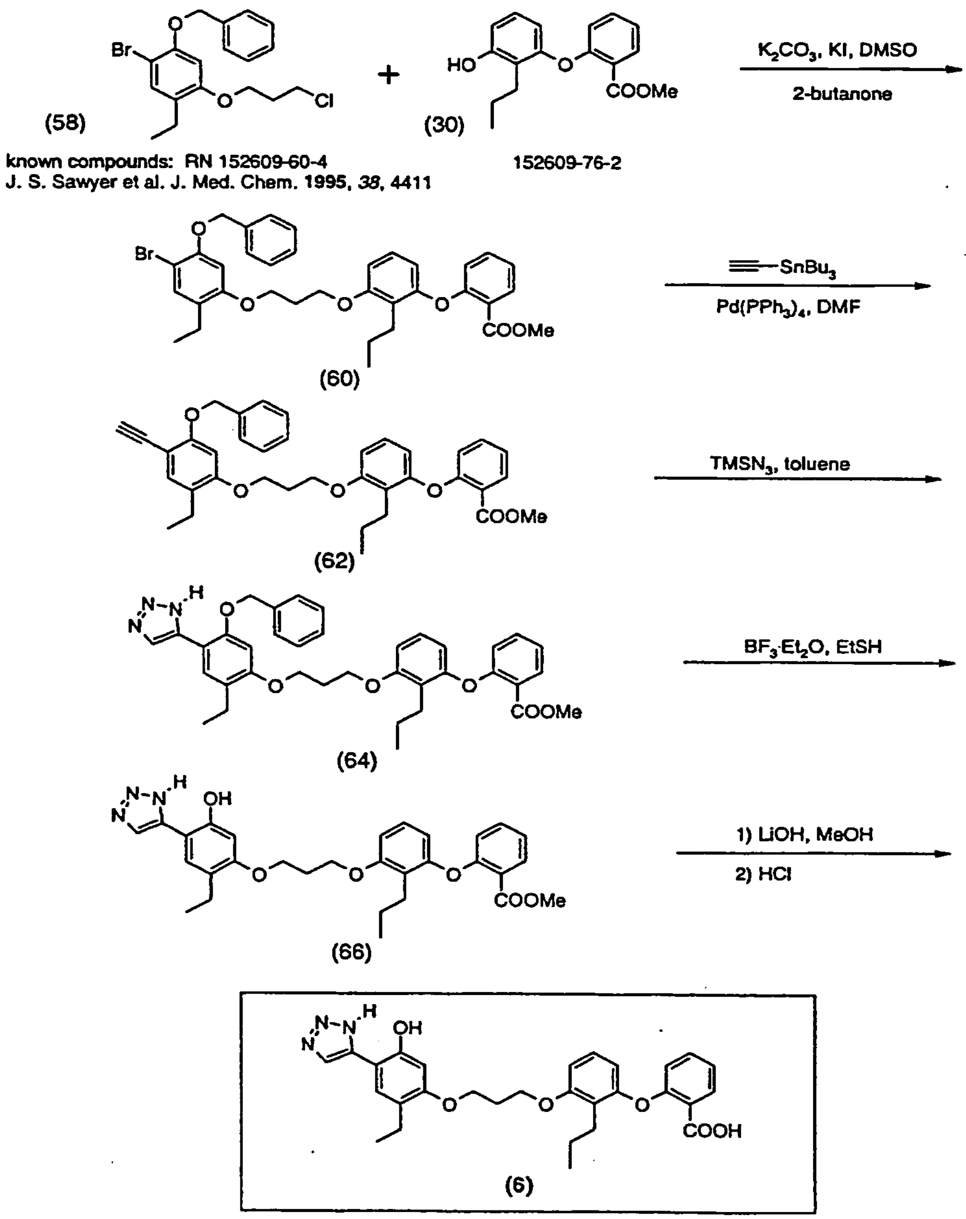

Me2N
COOMe
NH2OH, MeOH, H2O
(50)
N-O
BF3·Et2O, EtSH
(54)
OH
1) LiOH, MeOH
2) HCl
(56)
COOH
(5)

Treatment of enone (50) with hydroxylamine provides isoxazole (54), that is debenzylated with boron trifluoride etherate and ethanethiol to give isoxazole (56). Hydrolysis and protonation provides Example (5).

Scheme 6

The following scheme illustrates a process for making Example (6), a 5(4)-substituted 1,2,3-triazole LTB_4 receptor antagonist:

Scheme 6

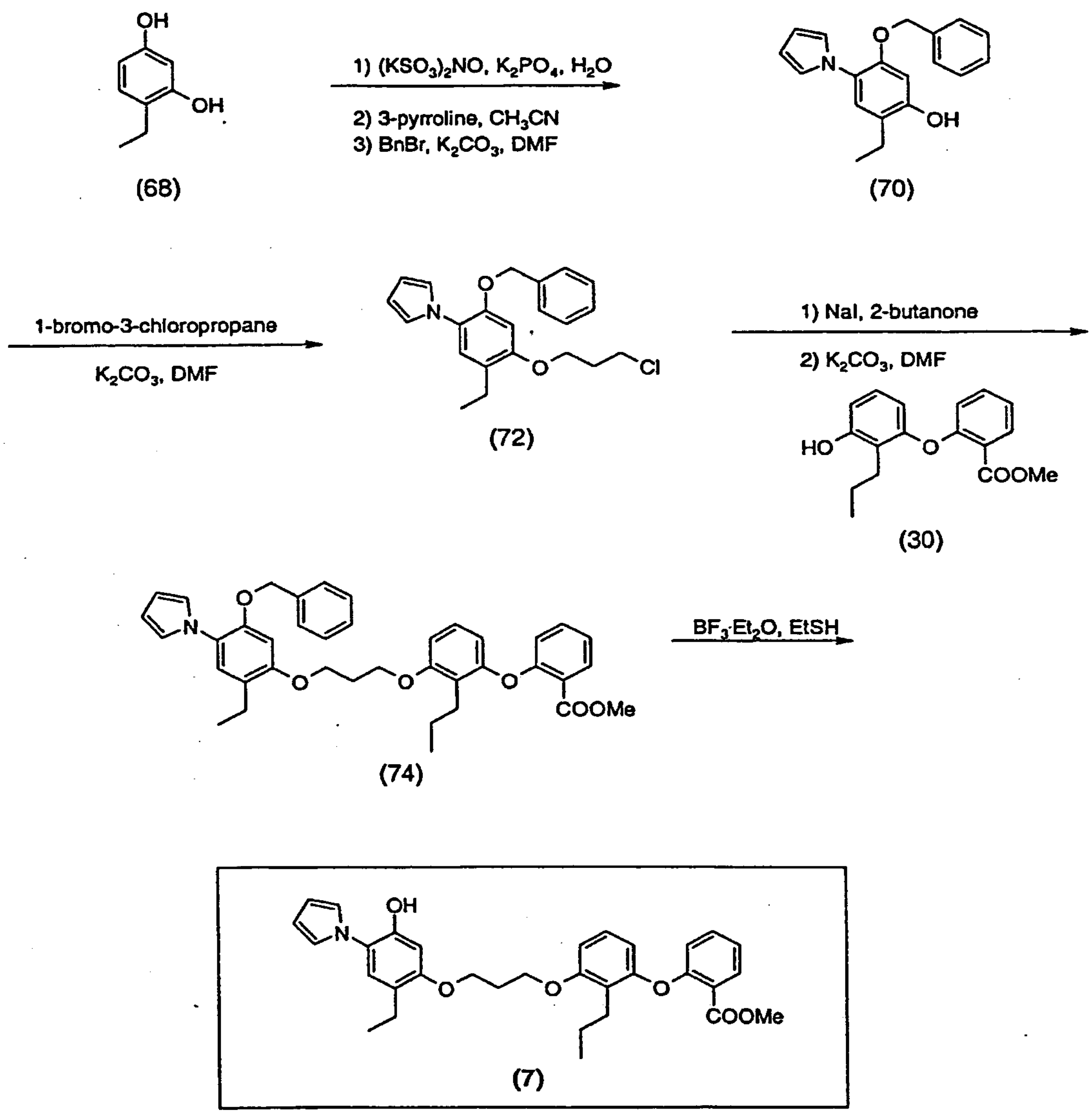

Br
O
O
Cl
(58)
+
HO
O
COOMe
(30)
K$_2$CO$_3$, KI, DMSO
2-butanone
known compounds: RN 152609-60-4
J. S. Sawyer et al. J. Med. Chem. 1995, 38, 4411
152609-76-2
(60)
COOMe
—SnBu$_3$
Pd(PPh$_3$)$_4$, DMF
(62)
TMSN$_3$, toluene
N-N-H
N
(64)
BF$_3$·Et$_2$O, EtSH
OH
(66)
1) LiOH, MeOH
2) HCl
COOH
(6)

Known phenol (30) is alkylated with known chloride (58) to give aryl bromide (60). Treatment of (60) with tri-*n*-butylethynyltin and a palladium catalyst gives alkyne (62). Heating (62) with trimethylsilyl azide provides triazole (64), that is debenzylated with boron trifluoride etherate and ethanethiol to give triazole (66). Hydrolysis and protonation provides Example (6).

Scheme 7

The following scheme illustrates a process for making Example (7), a 1-substituted pyrrole LTB_4 receptor antagonist:

Scheme 7



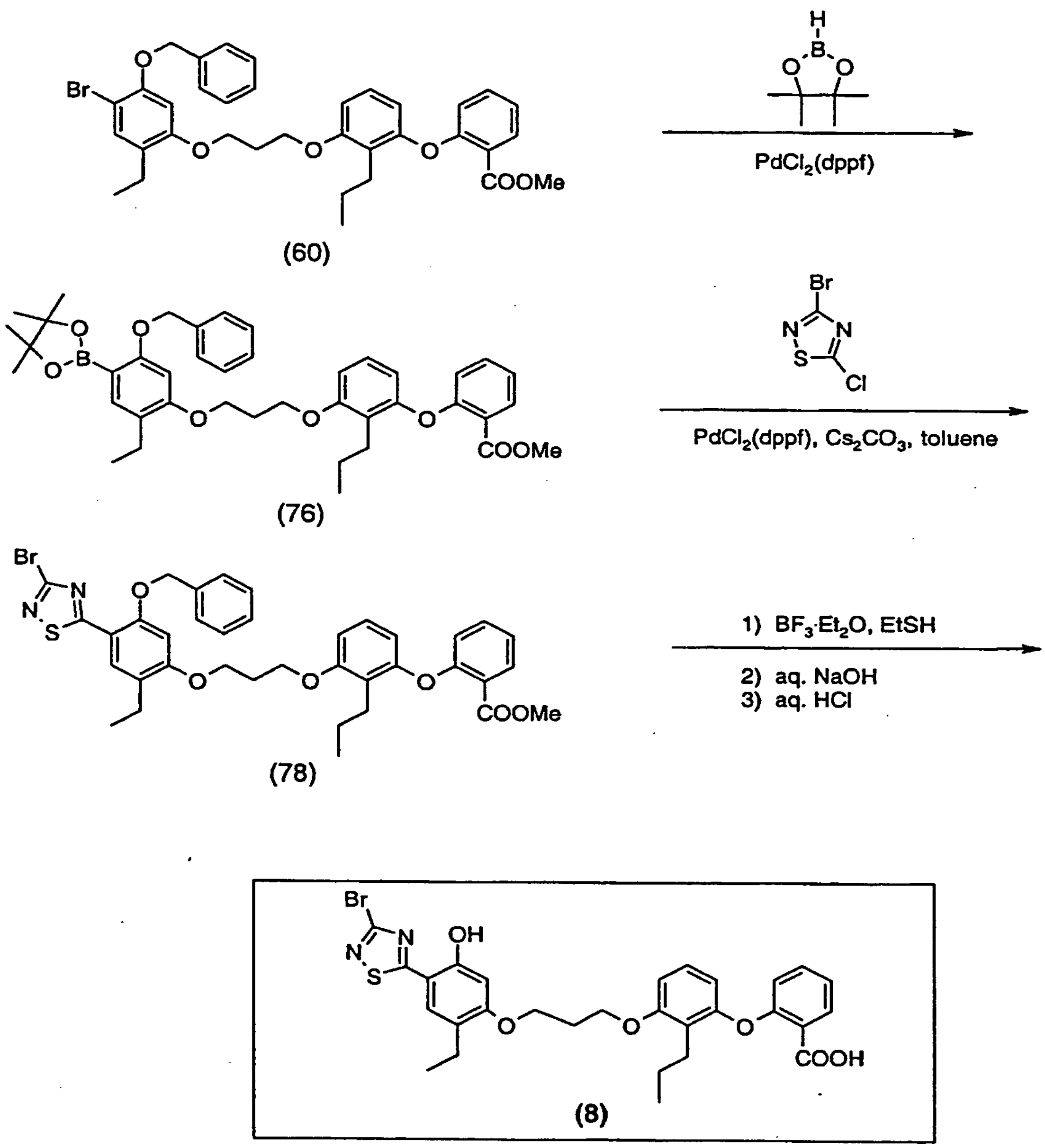
References for formation of 1-aryl substituted pyrroles: M. Mure and J. P. Klinman, J. Am. Chem. Soc. 1995, *117(34)*, 8698; Y. Lee et al. J. Am. Chem. Soc. 1996, *118(30)*, 7241

4-Ethylbenzene-1,3-diol (68) is treated with potassium nitrosodisulfonate followed by 3-pyrroline and benzylbromide and a base to provide pyrrole (70). Alkylation with 1-bromo-3-chloropropane gives chloride (72), that is used to alkylate phenol (30) to give pyrrole (74). Debenzylation with boron trifluoride etherate and ethanethiol provides Example (7).

Scheme 8

The following scheme illustrates a process for making Example (8), a 5-substituted 1,2,4-thiadiazole LTB_4 receptor antagonist:

Scheme 8

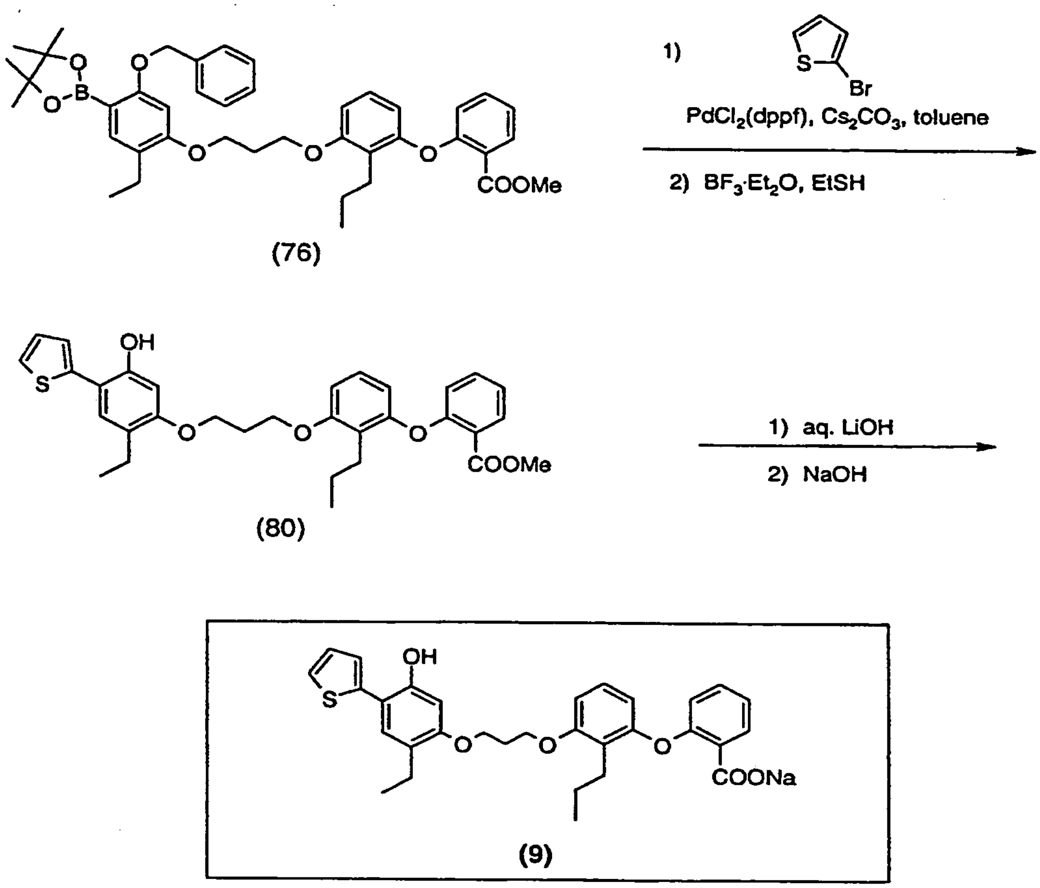

PdCl2(dppf)
(60)
PdCl2(dppf), Cs2CO3, toluene
(76)
1) BF3·Et2O, EtSH
2) aq. NaOH
3) aq. HCl
(78)
(8)

The palladium-catalyzed addition of 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane to bromide (60) gives boronic ester (76). The palladium-catalyzed addition of 3-bromo-5-chloro-1,2,4-thiadiazole to (76) gives ester (78). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, gives Example (8).

Scheme 9

The following scheme illustrates a process for making Example (9), a 2-substituted thiophene LTB_4 receptor antagonist:

Scheme 9

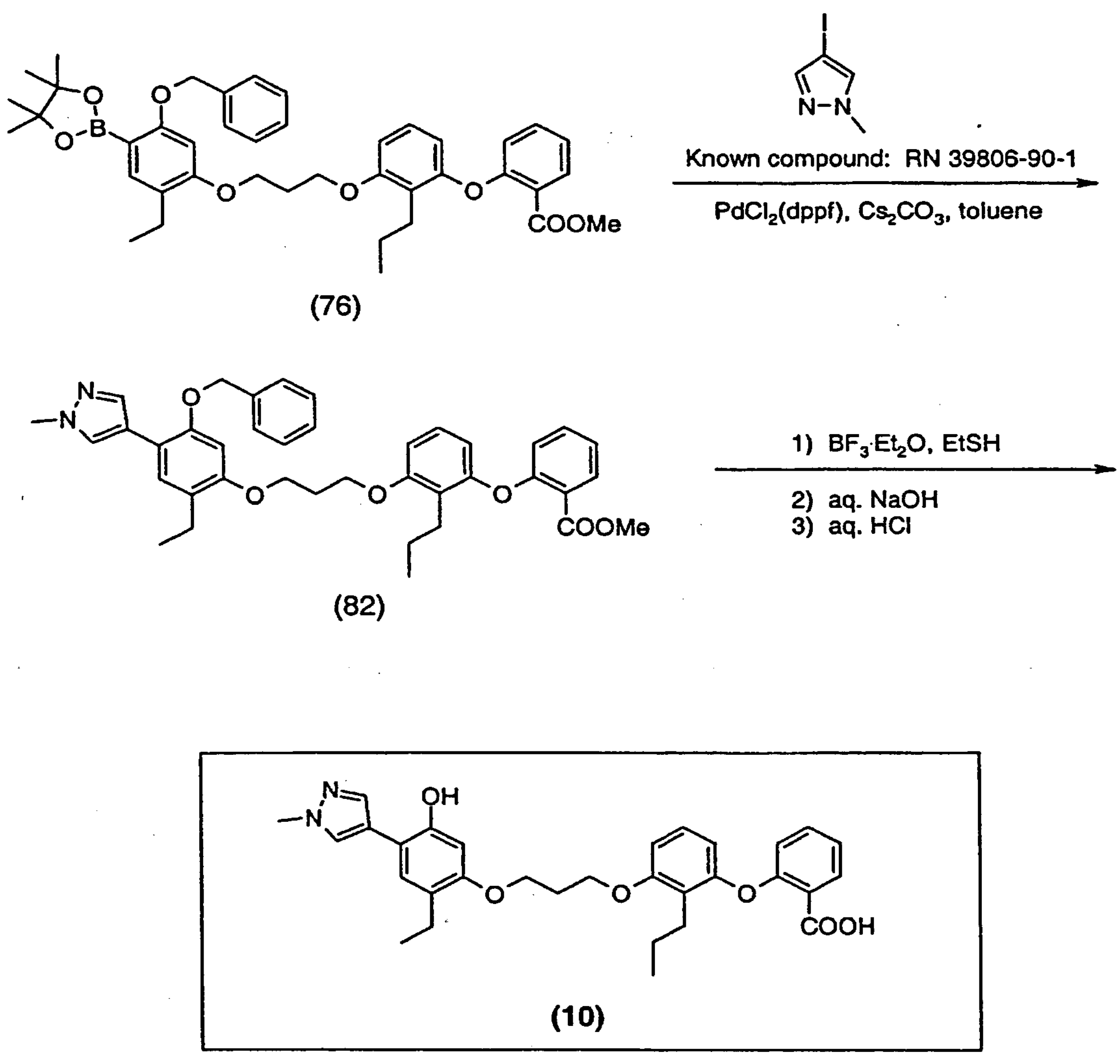


The palladium-catalyzed addition of boronic ester (76) to 2-bromothiophene, followed by debenzylation with boron trifluoride etherate and ethanethiol, provides thiophene (80). Hydrolysis and salt formation provides Example (9).

Scheme 10

The following scheme illustrates a process for making Example (10), a 4-substituted pyrazole LTB_4 receptor antagonist:

Scheme 10

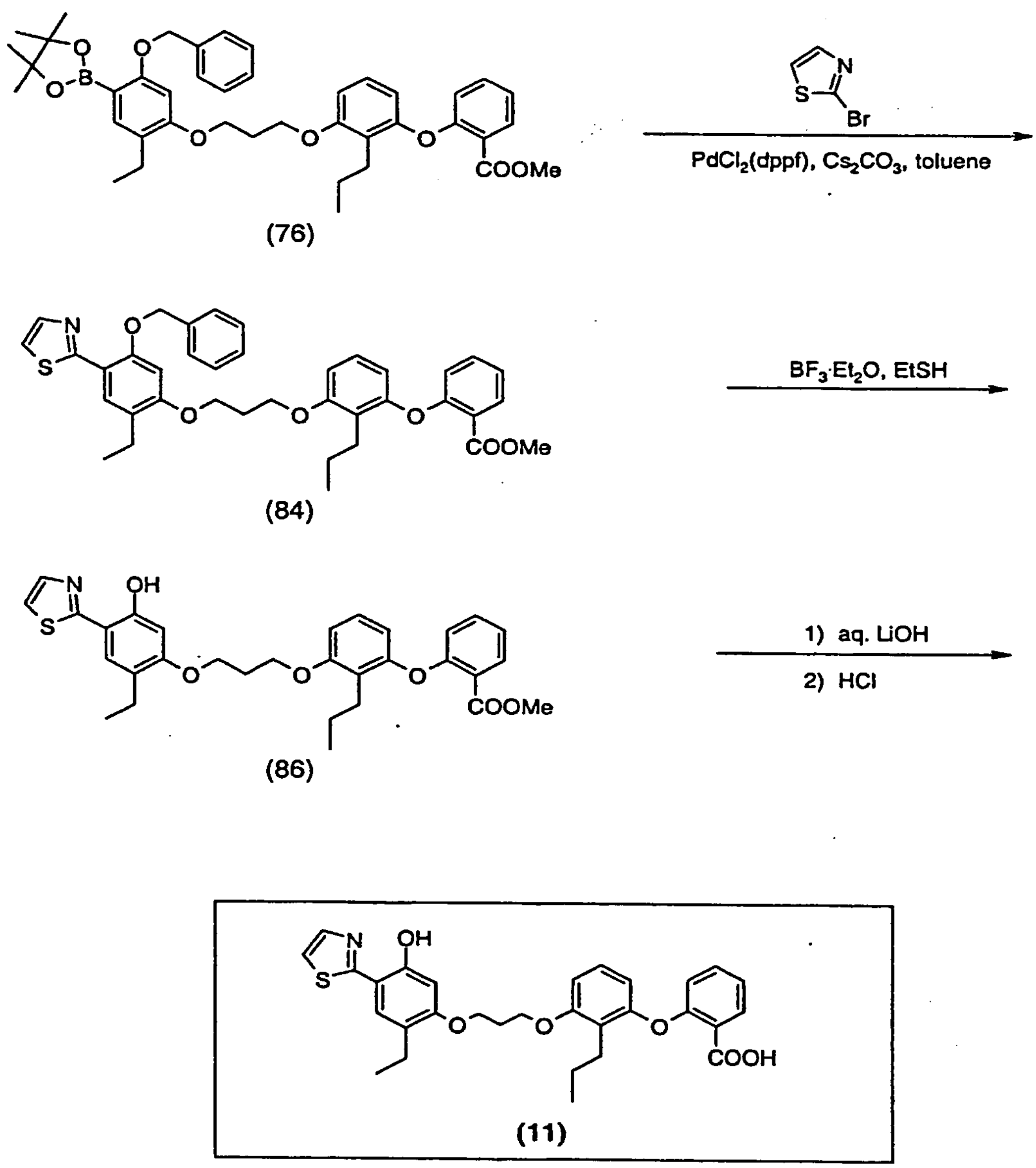

Known compound: RN 39806-90-1
PdCl2(dppf), Cs2CO3, toluene
COOMe
(76)
1) BF3·Et2O, EtSH
2) aq. NaOH
3) aq. HCl
COOMe
(82)
OH
COOH
(10)

The palladium-catalyzed addition of boronic ester (76) to 1-methyl-4-iodopyrazole provides pyrazole (82). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, provides Example (10).

Scheme 11

The following scheme illustrates a process for making Example (11), a 2-substituted thiazole LTB_4 receptor antagonist:

Scheme 11

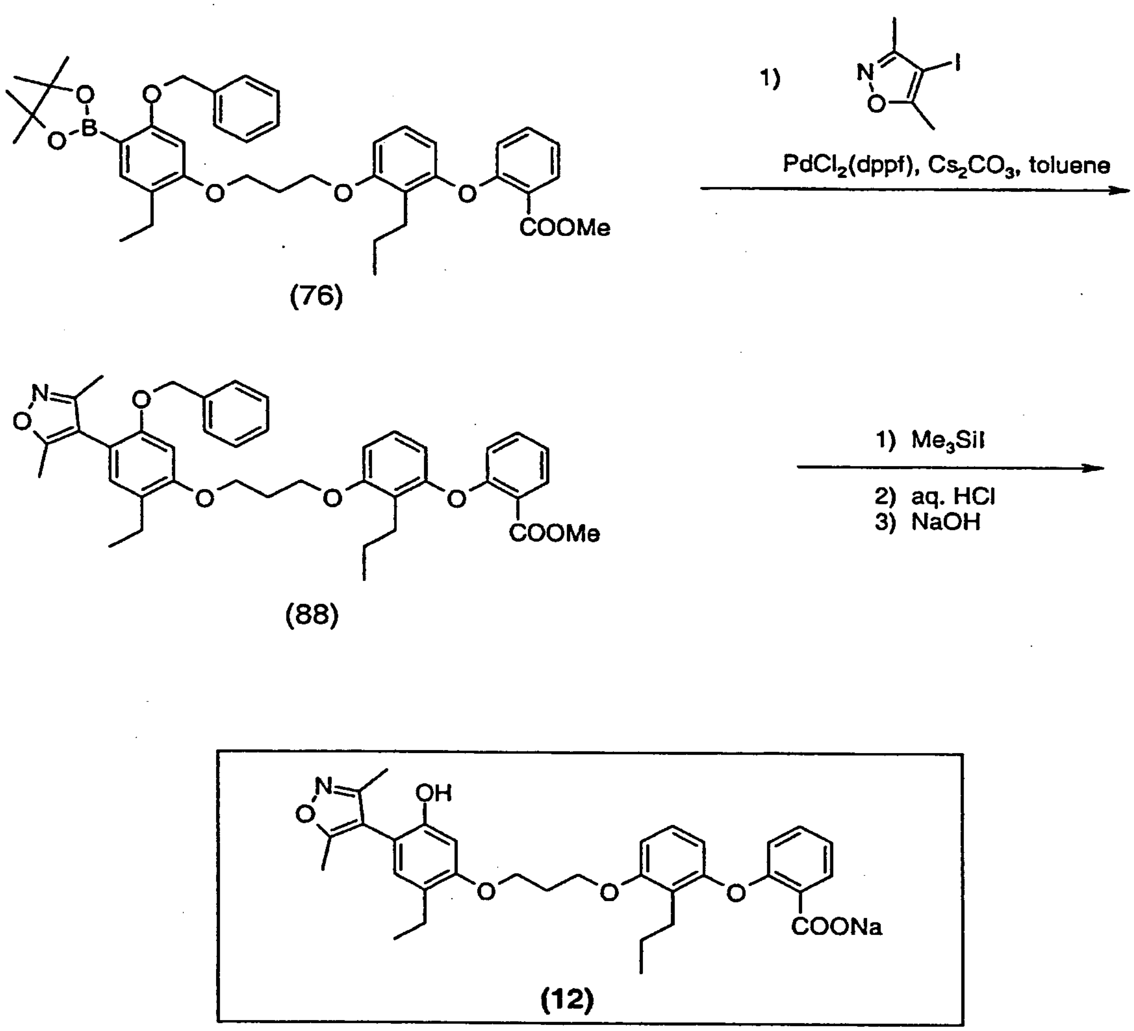

Br
PdCl$_2$(dppf), Cs$_2$CO$_3$, toluene
COOMe
(76)
COOMe
BF$_3$·Et$_2$O, EtSH
(84)
OH
COOMe
1) aq. LiOH
2) HCl
(86)
OH
COOH
(11)

The palladium-catalyzed addition of boronic ester (76) to 2-bromothizaole provides thiazole (84). Debenzylation with boron trifluoride etherate and ethanethiol gives thiazole (86). Hydrolysis and protonation provides Example (11).

Scheme 12

The following scheme illustrates a process for making Example (12), a 4-substituted isoxazole LTB_4 receptor antagonist:

Scheme 12

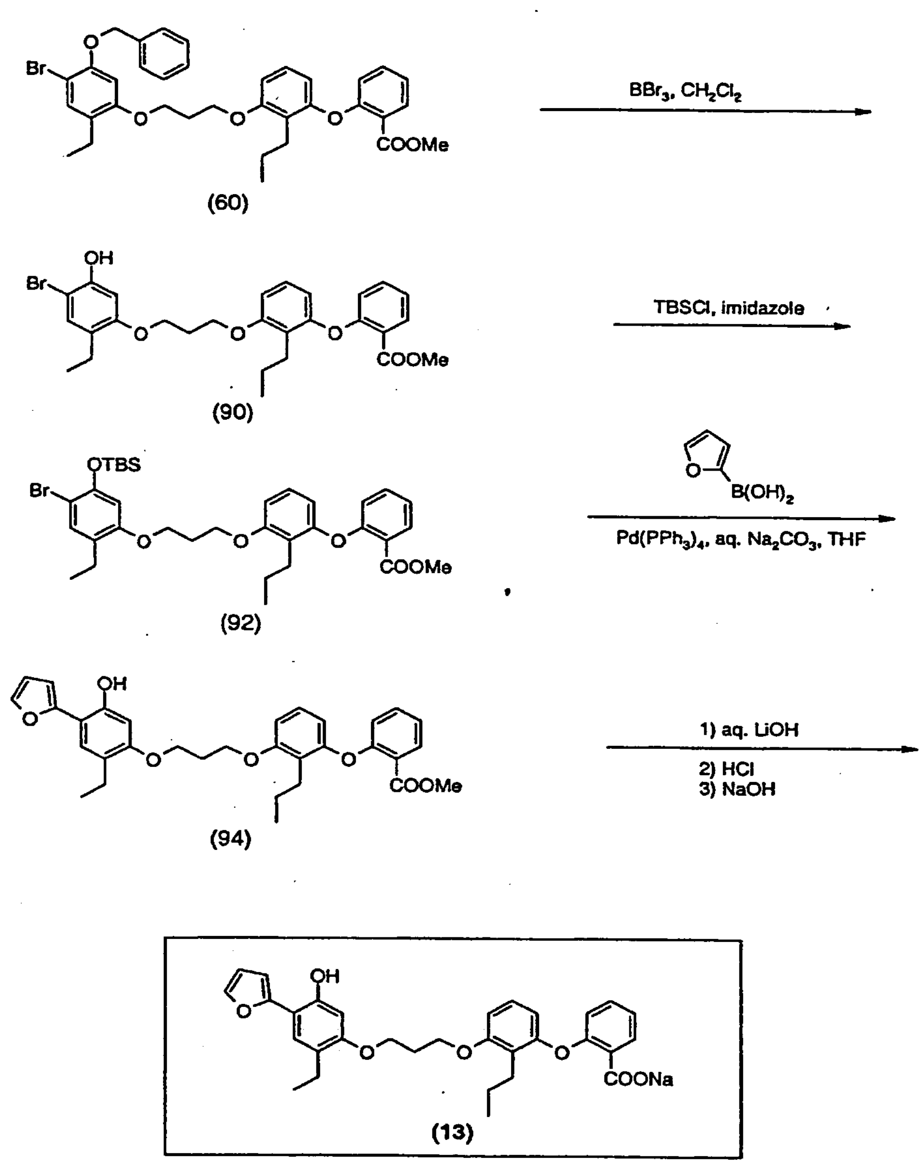

(76)
1)
PdCl$_2$(dppf), Cs$_2$CO$_3$, toluene
COOMe
(88)
1) Me$_3$SiI
2) aq. HCl
3) NaOH
COOMe
OH
COONa
(12)

The palladium-catalyzed addition of boronic ester (76) to 3,5-dimethyl-4-iodoisoxazole provides oxazole (88). Debenzylation with trimethylsilyl iodide, followed by hydrolysis and salt formation, provides Example (12).

Scheme 13

The following scheme illustrates a process for making Example (13), a 2-substituted furan LTB_4 receptor antagonist:

Scheme 13

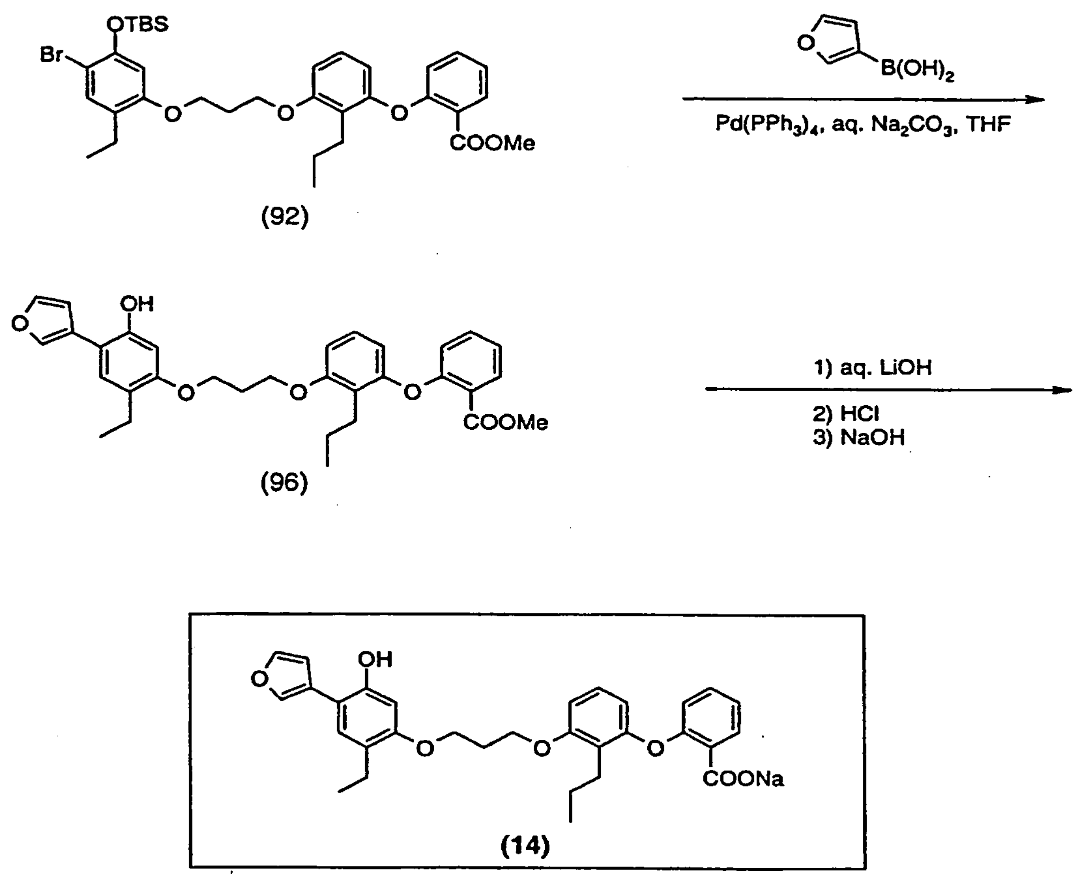

BBr$_3$, CH$_2$Cl$_2$
(60)
TBSCl, imidazole
(90)
B(OH)$_2$
Pd(PPh$_3$)$_4$, aq. Na$_2$CO$_3$, THF
(92)
1) aq. LiOH
2) HCl
3) NaOH
(94)
(13)

Debenzylation of bromide (60) with boron tribromide provides phenol (90), that is treated with *tert*-butyldimethylsilyl chloride and imidazole to give silyl ether (92). The palladium-catalyzed addition of (92) to furan-2-boronic acid provides furan (94). Hydrolysis and salt formation gives Example (13).

Scheme 14

The following scheme illustrates a process for making Example (14), a 3-substituted furan LTB_4 receptor antagonist:

Scheme 14

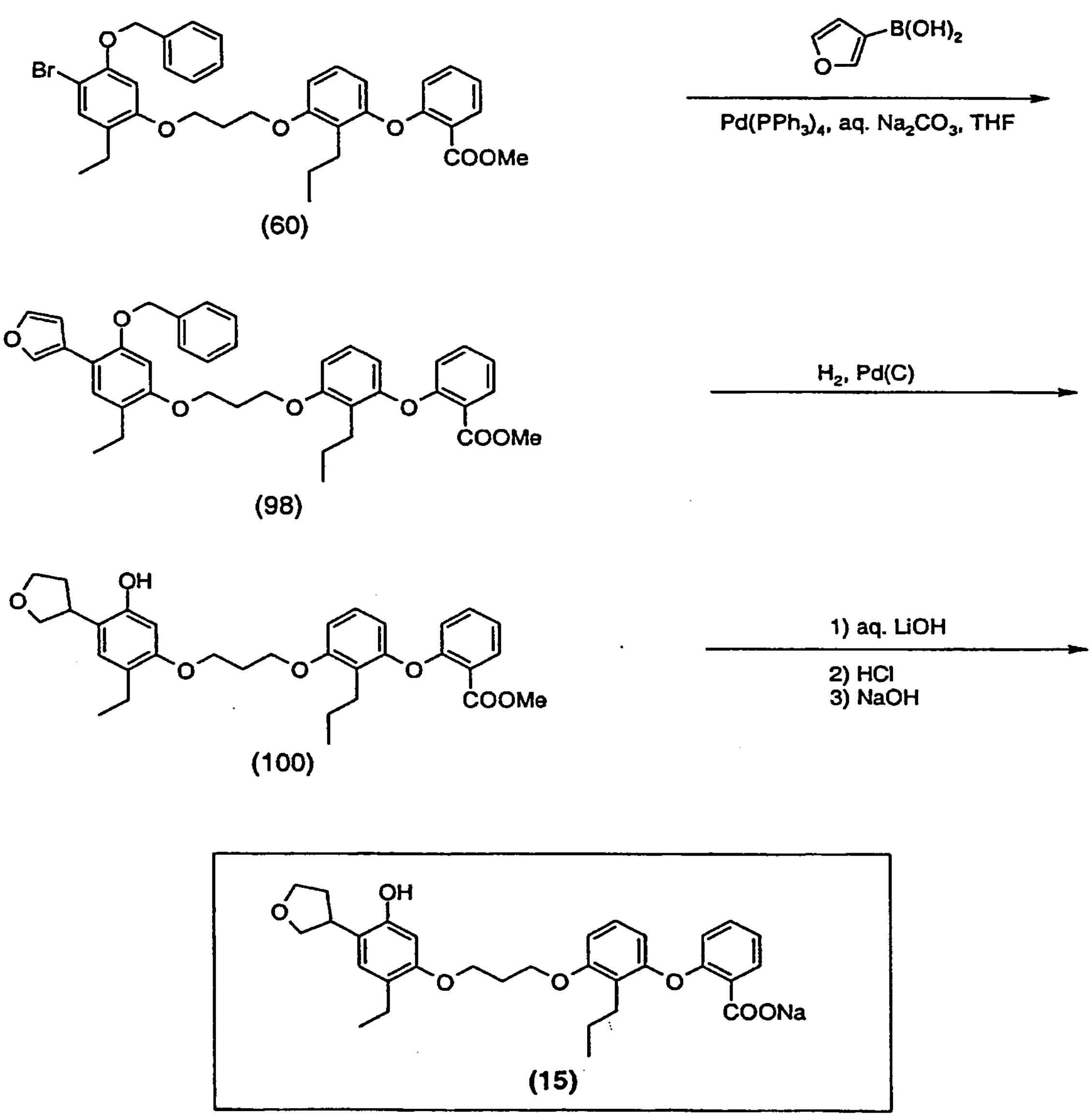


The palladium-catalyzed addition of (92) to furan-3-boronic acid provides furan (96). Hydrolysis and salt formation gives Example (14).

Scheme 15

The following scheme illustrates a process for making Example (15), a 3-substituted tetrahydrofuran LTB_4 receptor antagonist:

Scheme 15

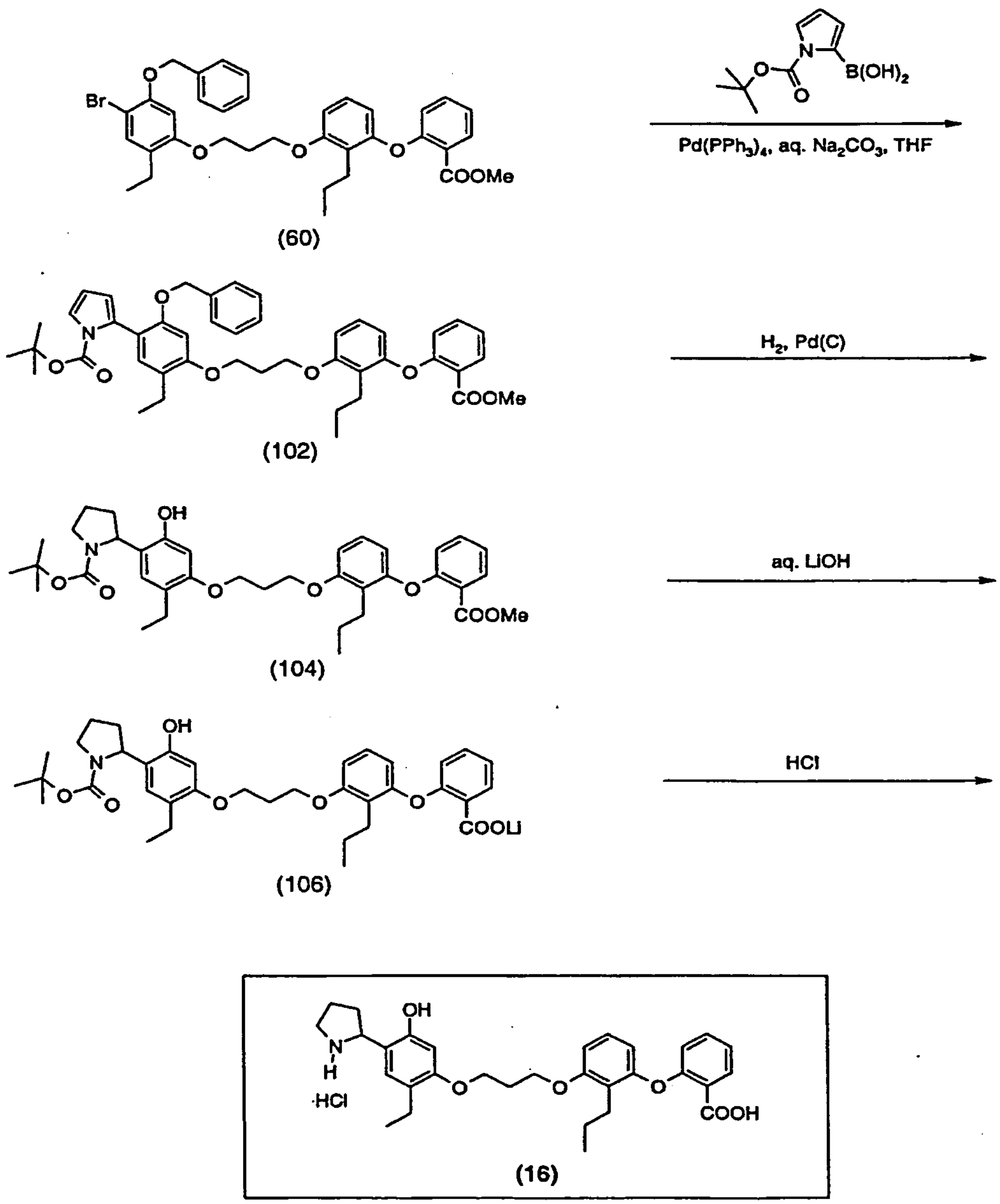

B(OH)$_2$
Br
COOMe
(60)
Pd(PPh$_3$)$_4$, aq. Na$_2$CO$_3$, THF
(98)
H$_2$, Pd(C)
OH
(100)
1) aq. LiOH
2) HCl
3) NaOH
COONa
(15)

The palladium-catalyzed addition of bromide (60) to furan-3-boronic acid provides furan (98). Hydrogenation over a palladium catalyst gives tetrahydrofuran (100). Hydrolysis and salt formation gives Example (15).

Scheme 16

The following scheme illustrates a process for making Example (16), a 2-substituted pyrrolidine LTB_4 receptor antagonist:

Scheme 16

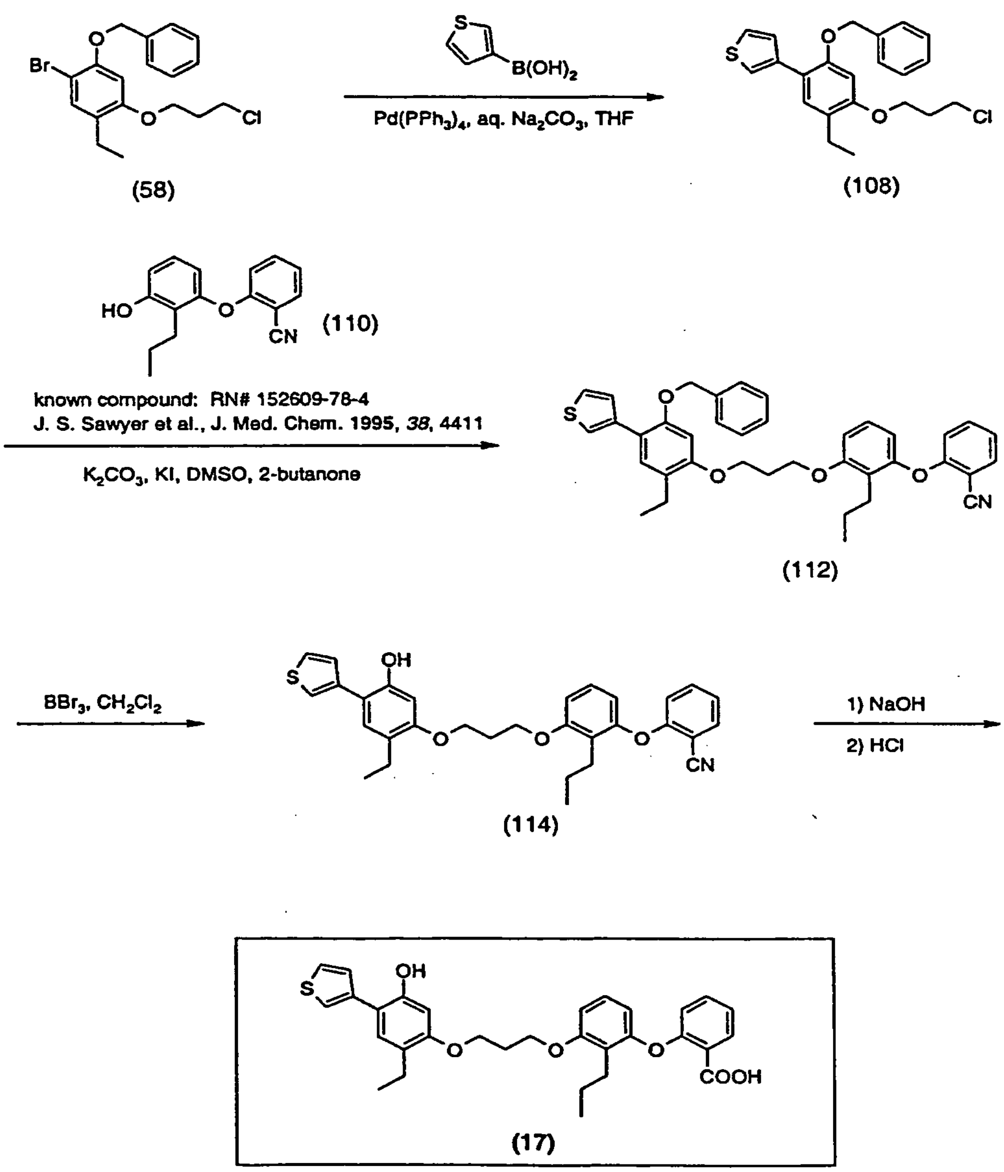

Br
COOMe
B(OH)$_2$
$Pd(PPh_3)_4$, aq. Na_2CO_3, THF
(60)
COOMe
H_2, Pd(C)
(102)
OH
COOMe
aq. LiOH
(104)
OH
COOLi
HCl
(106)
OH
·HCl
COOH
(16)

The palladium-catalyzed addition of bromide (60) to N-boc pyrrole-2-boronic acid provides pyrrole (102). Hydrogenation over a palladium catalyst gives pyrrolidine (104). Hydrolysis and salt formation gives pyrrolidine (106). Treatment with hydrochloric acid provides Example (16) as the hydrochloride salt.

Scheme 17

The following scheme illustrates a process for making Example (17), a 3-substituted thiophene LTB_4 receptor antagonist:

Scheme 17

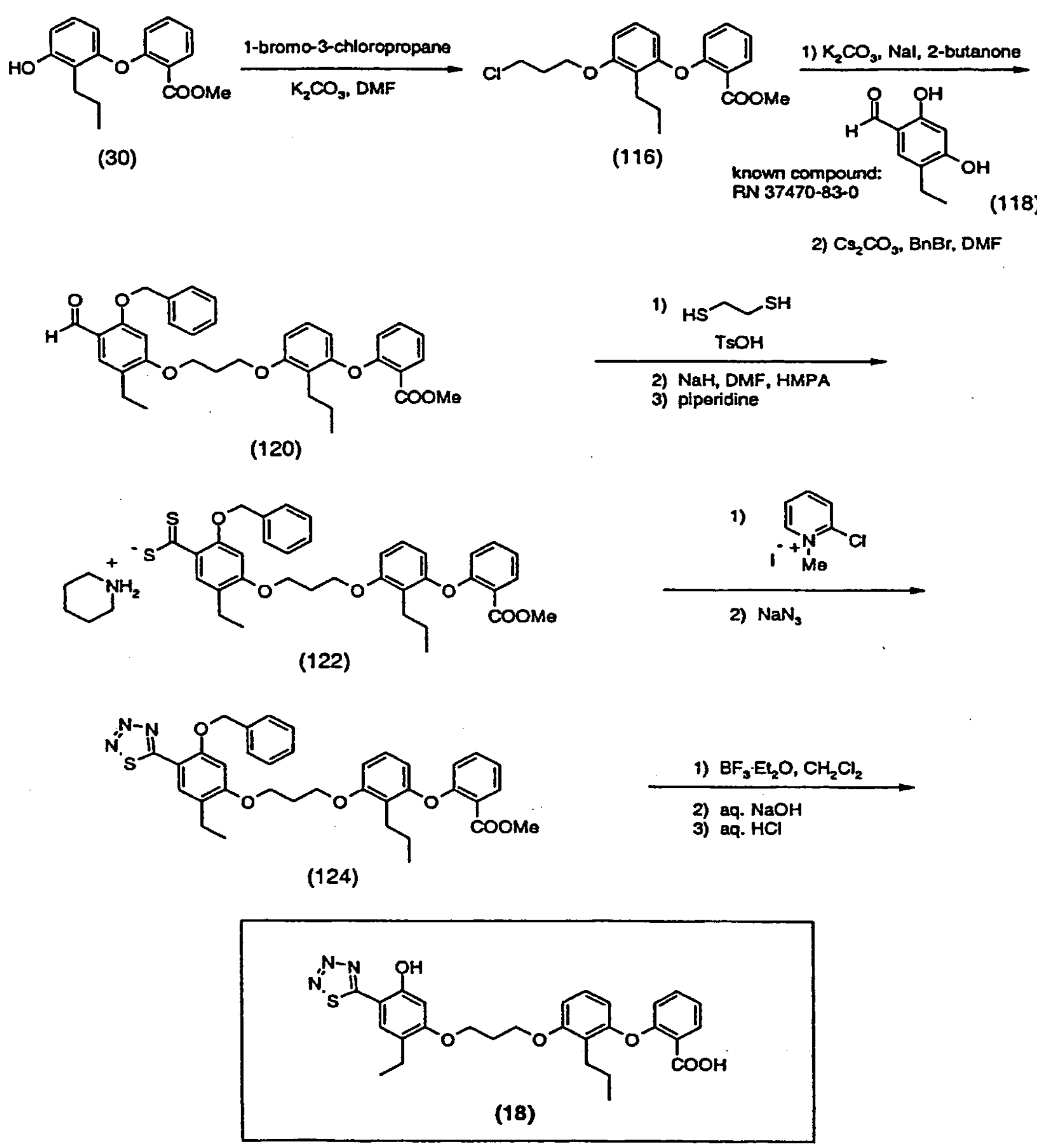

B(OH)$_2$
Pd(PPh$_3$)$_4$, aq. Na$_2$CO$_3$, THF
(58)
(108)
(110)
known compound: RN# 152609-78-4
J. S. Sawyer et al., J. Med. Chem. 1995, *38*, 4411
K$_2$CO$_3$, KI, DMSO, 2-butanone
(112)
BBr$_3$, CH$_2$Cl$_2$
(114)
1) NaOH
2) HCl
(17)

The palladium-catalyzed addition of bromide (58) to thiophene-3-boronic acid provides thiophene (108). Alkylation of known phenol (110) with (108) catalyzed by base provides thiophene (112). Debenzylation with boron tribromide gives thiophene (114). Hydrolysis and protonation provide Example (17).

Scheme 18

The following scheme illustrates a process for making Example (18), a 5-substituted 1,2,3,4-thiatriazole LTB_4 receptor antagonist:

Scheme 18



Reference for formation of dithioacids: N. C. Gonnella et al. Syn. Commun. 1979, 17

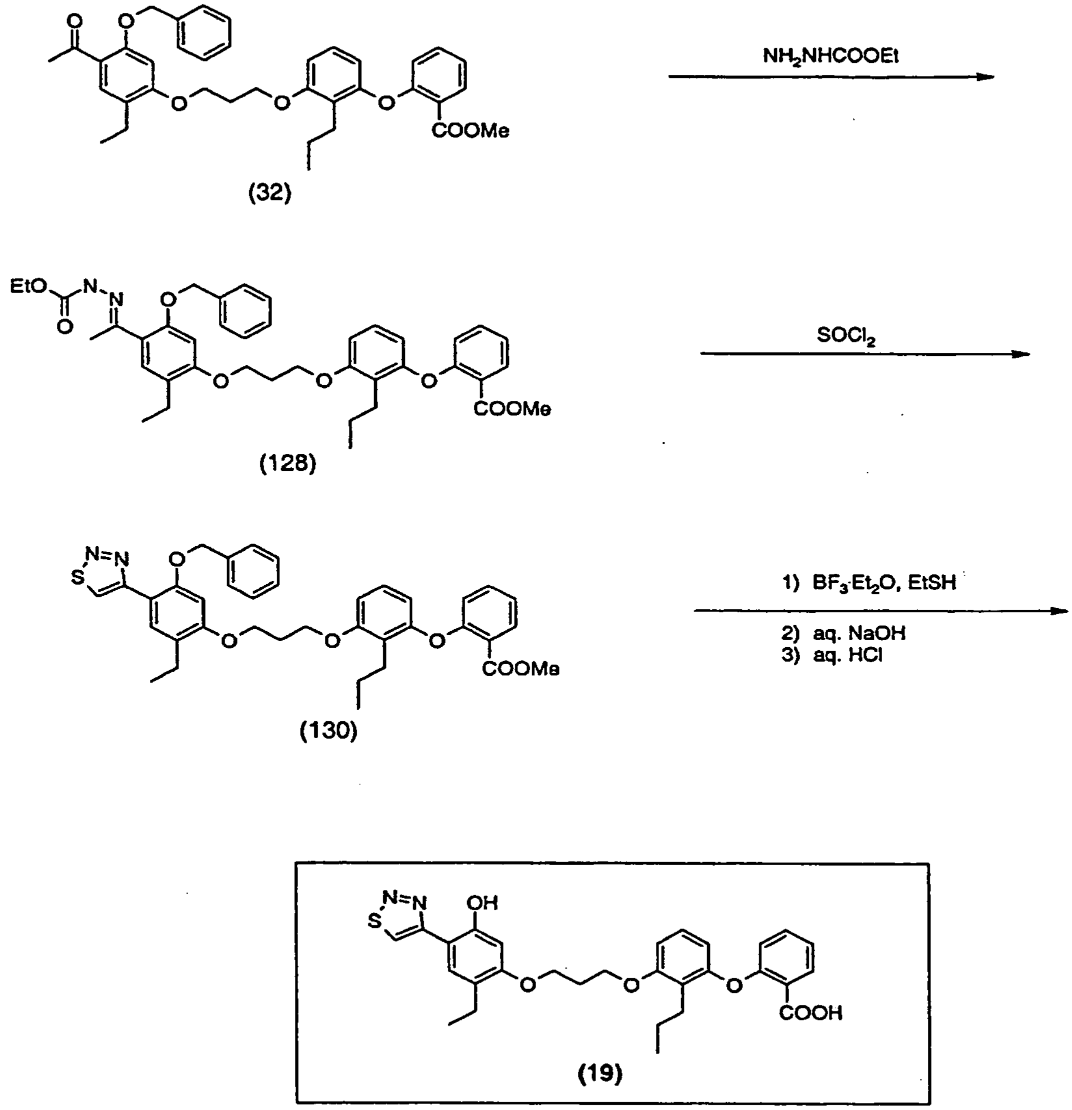
Reference for formation of 5-substituted 1,2,3,4-thiatriazoles from dithioacids: S. I. Ikeda et al., Synthesis 1990, 415

Phenol (30) is alkylated with 1-bromo-3-chloropropane to give chloride (116), that is in turn to be treated with known aldehyde (118) and a base, followed by benzylation with benzyl bromide and a base, to provide aldehyde (120). From aldehyde (120) is made the thioacetal by treatment with 1,2-ethanedithiol. The resulting thioacetal is then to be treated with base to provide the thioacid. Treatment with piperidine makes piperidinium salt (122). By the teaching of Ikeda, infra, (the disclosure of which is incorporated herein by reference) treatment of (122) with 2-chloropyridinium methyl iodide followed by azide ion will give the 1,2,3,4-thiatriazole (124). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, will provide the product of Example (18).

Scheme 19

The following scheme illustrates a process for making Example (19), a 4-substituted 1,2,3-thiadiazole LTB_4 receptor antagonist:

Scheme 19



(19)

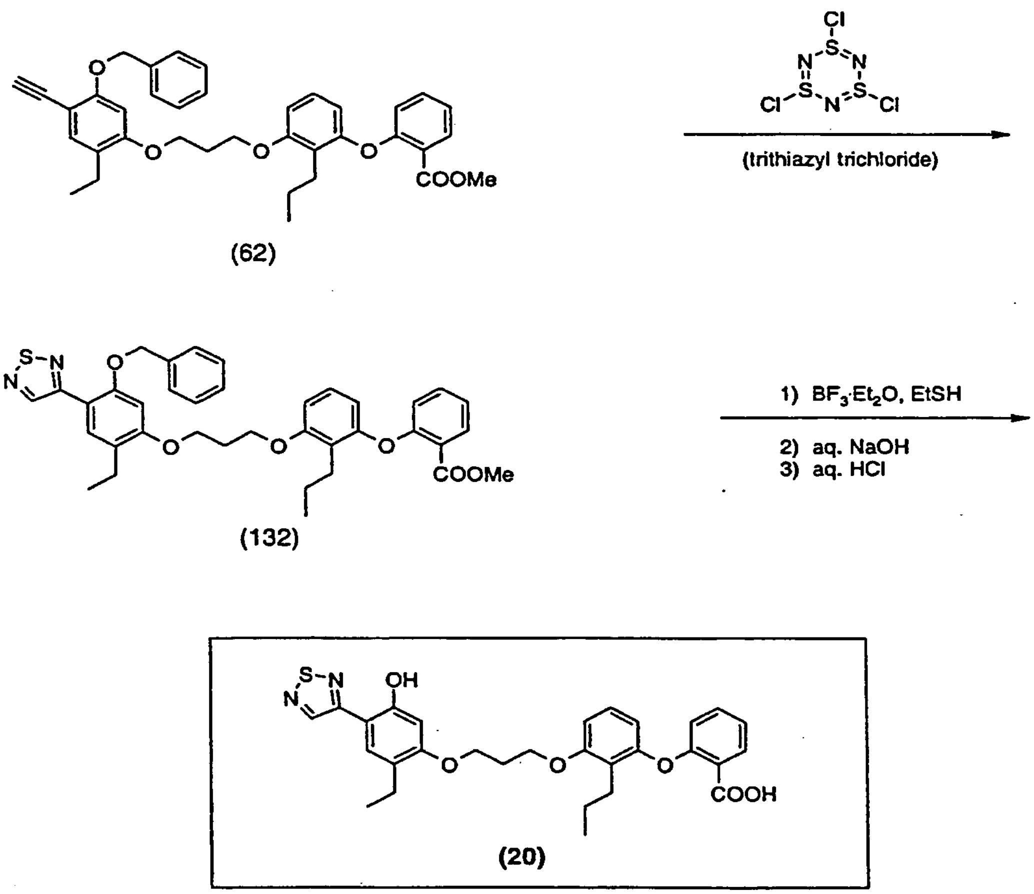
Reference for 1,2,3-thiadiazole formation: E. W. Thomas et al., J. Med. Chem. 1985, *28*, 442.

Treatment of acetophenone (32) with ethyl carbazate will give the hydrazone (128). Use of thionyl chloride by the method of Thomas et. al. (infra., the disclosure of which is incorporated herein by reference) will give an intermediate 1,2,3-thiadiazole (130), that is to be debenzylated with boron trifluoride etherate and ethanethiol, then hydrolyzed and protonated to give the product of Example (19).

Scheme 20

The following scheme illustrates a process for making Example (20), a 3-substituted 1,2,5-thiadiazole LTB_4 receptor antagonist:

Scheme 20



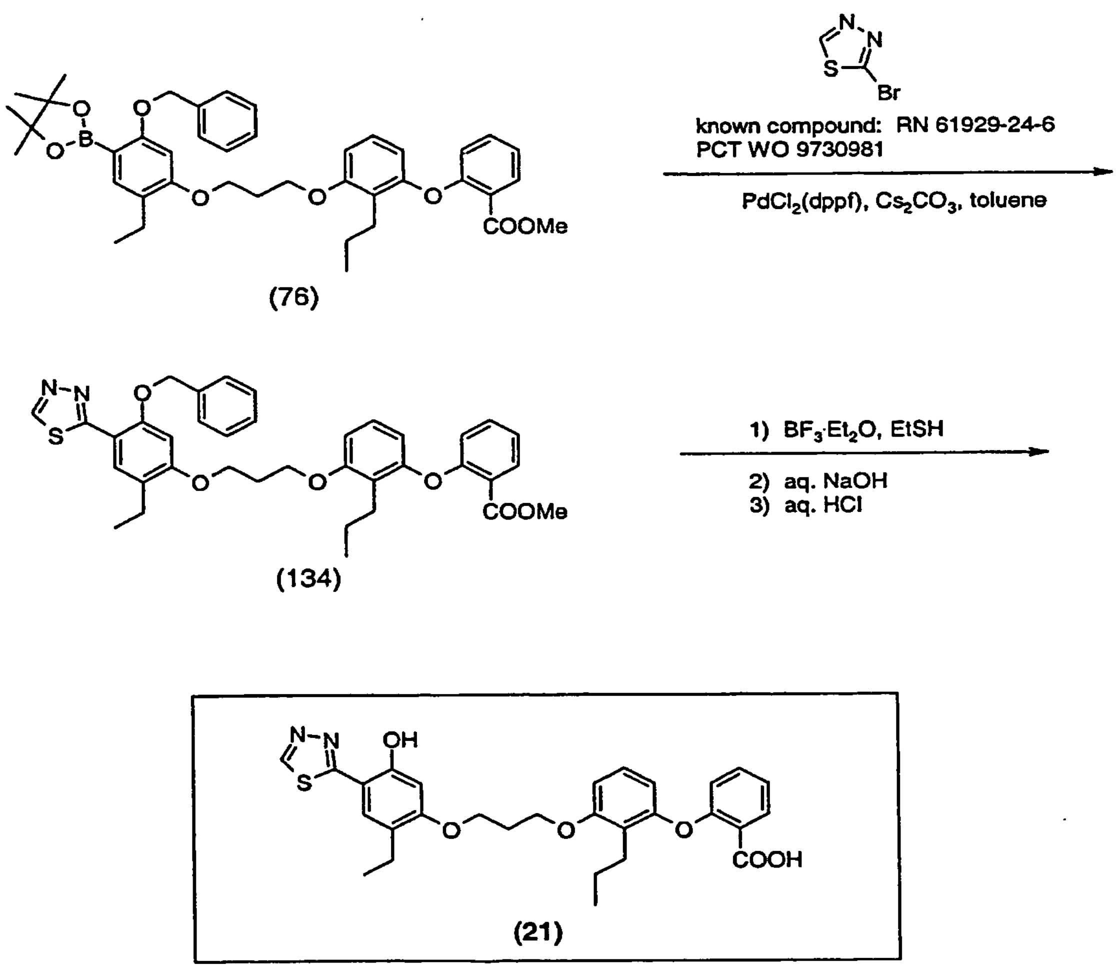
Reference for 1,2,5-thiadiazole formation: E. W. Thomas et al., J. Med. Chem. 1985, *28*, 442.

Alkyne (62) is to be treated with trithiazyl trichloride by the method of Thomas et. al. (infra., the disclosure of which is incorporated herein by reference) to provide thiadiazole (132). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, will provide the product of Example (20).

Scheme 21

The following scheme illustrates a process for making Example (21), a 2-substituted 1,3,4-thiadiazole LTB_4 receptor antagonist:

Scheme 21



(76)

(134)

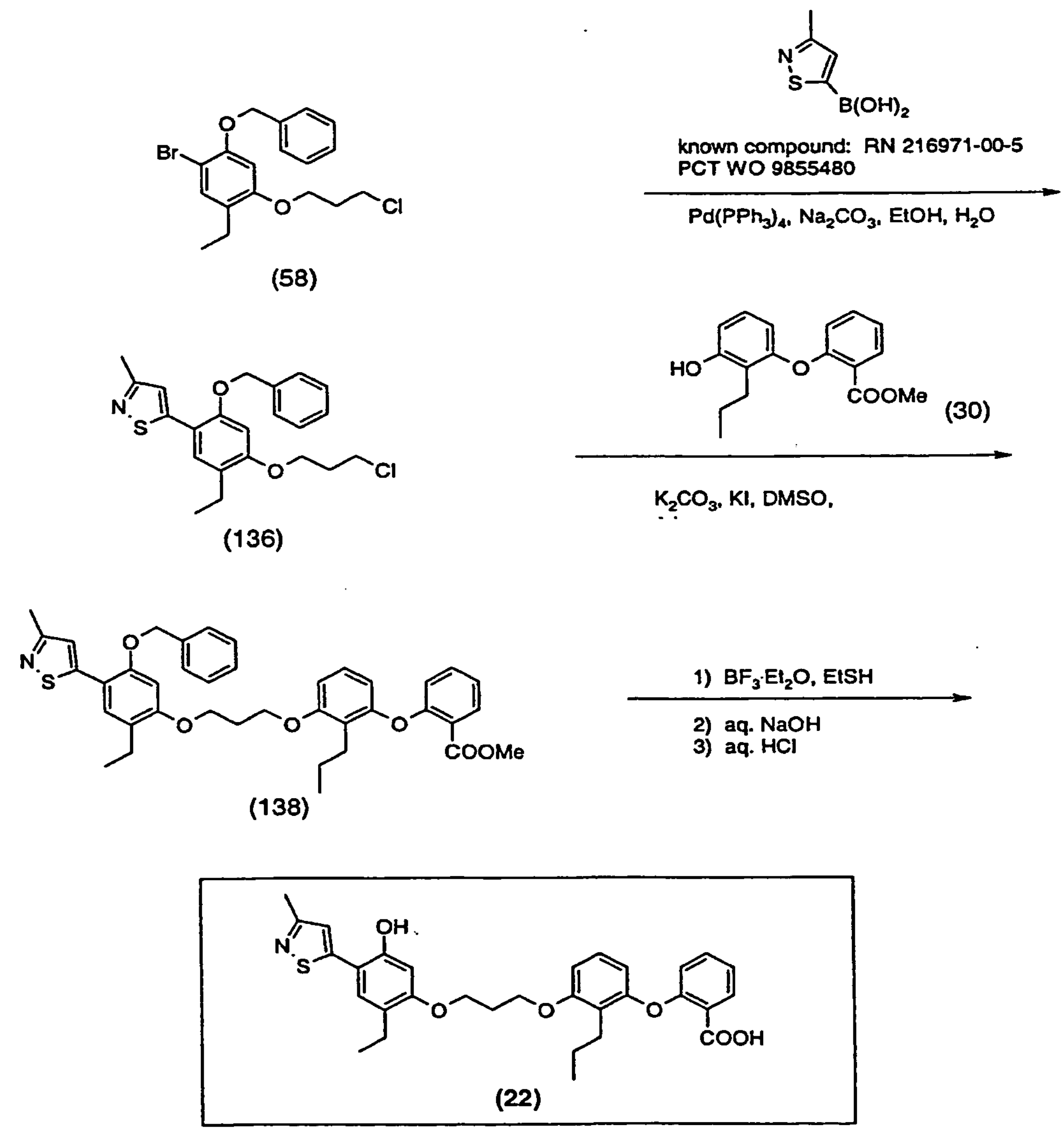
(21)

The palladium-catalyzed addition of boronic ester (76) to 2-bromo-1,3,4-thiadiazole will provide ester (134). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, will provide the product of Example (21).

Scheme 22

The following scheme illustrates a process for making Example (22), a 5-substituted isothiazole LTB_4 receptor antagonist:

Scheme 22

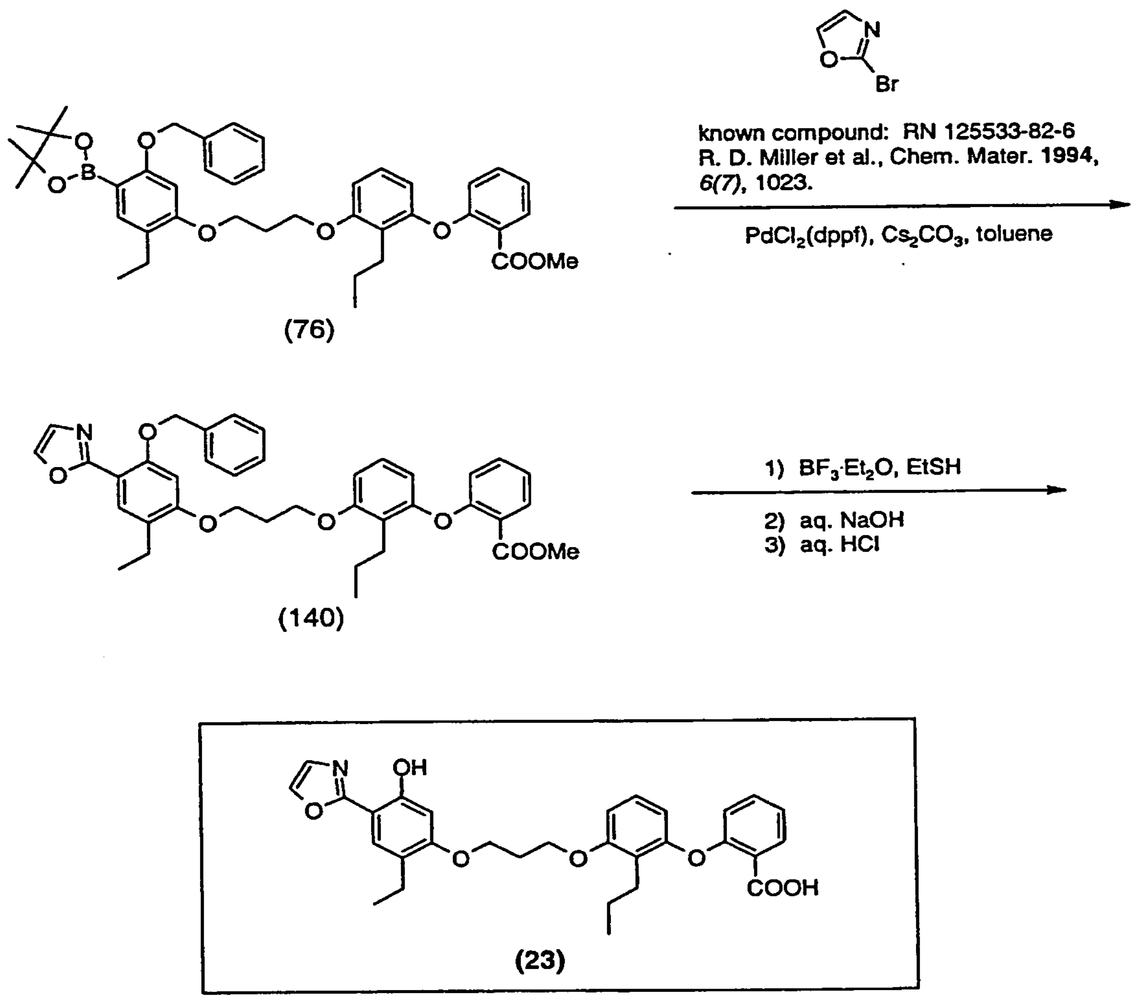


The palladium-catalyzed addition of bromide (58) to 3-methylisothiazole-5-boronic acid will provide isothiazole (136). Alkylation of phenol (30) with (136) catalyzed by base will provide isothiazole (138). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, will provide the product of Example (22).

Scheme 23

The following scheme illustrates a process for making Example (23), a 2-substituted oxazole LTB_4 receptor antagonist:

Scheme 23

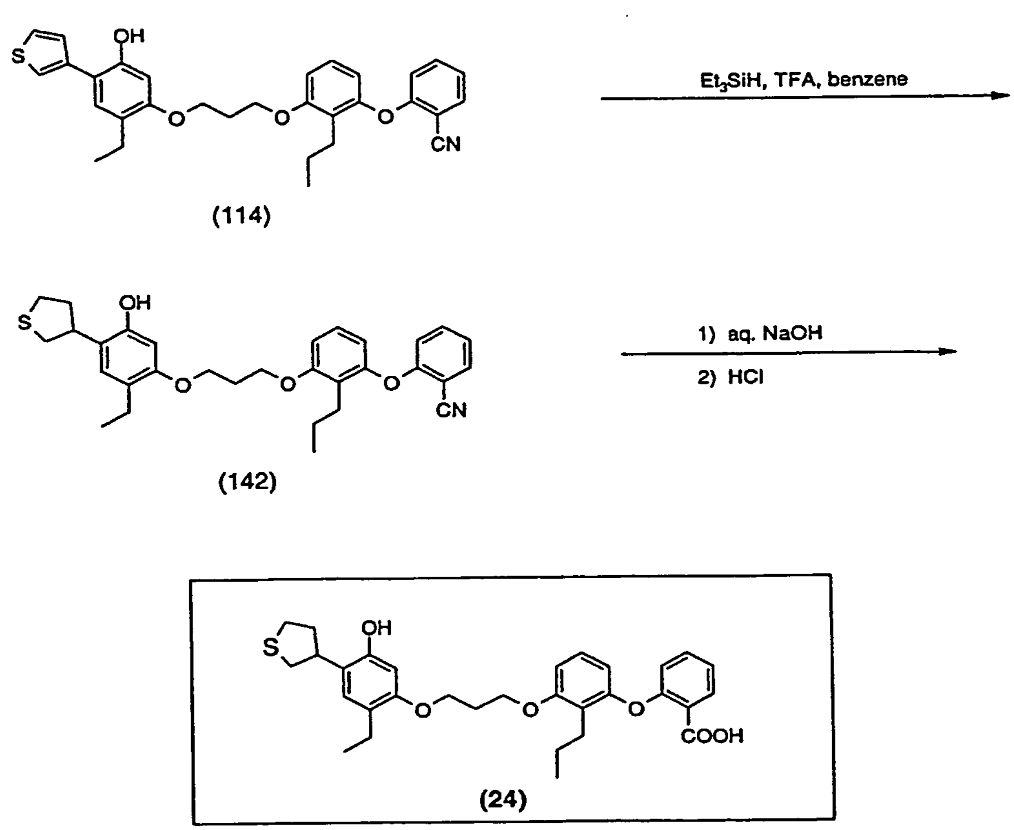


The palladium-catalyzed addition of boronic ester (76) to 2-bromooxazole will provide oxazole (140). Debenzylation with boron trifluoride etherate and ethanethiol, followed by hydrolysis and protonation, provides the product of Example (23).

Scheme 24

The following scheme illustrates a process for making Example (24), a 3-substituted thiophane LTB_4 receptor antagonist:

Scheme 24



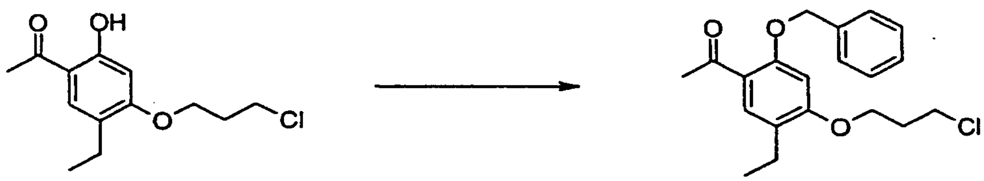
Reference for formation of tetrahydrothiophenes: D. N. Kursanov et al. Tetrahedron 1975, *31*, 311

Thiophene (114) may be reduced in the presence of triethylsilane and trifluoroacetic acid by the method of Kursanov et. al. (infra., the disclosure of which is incorporated herein by reference) to provide the thiophane (142). Hydrolysis and protonation provides the product of Example (24).

V. PREPARATIVE EXAMPLES 1 TO 17:

Example 1

Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-oxazol-4-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid.



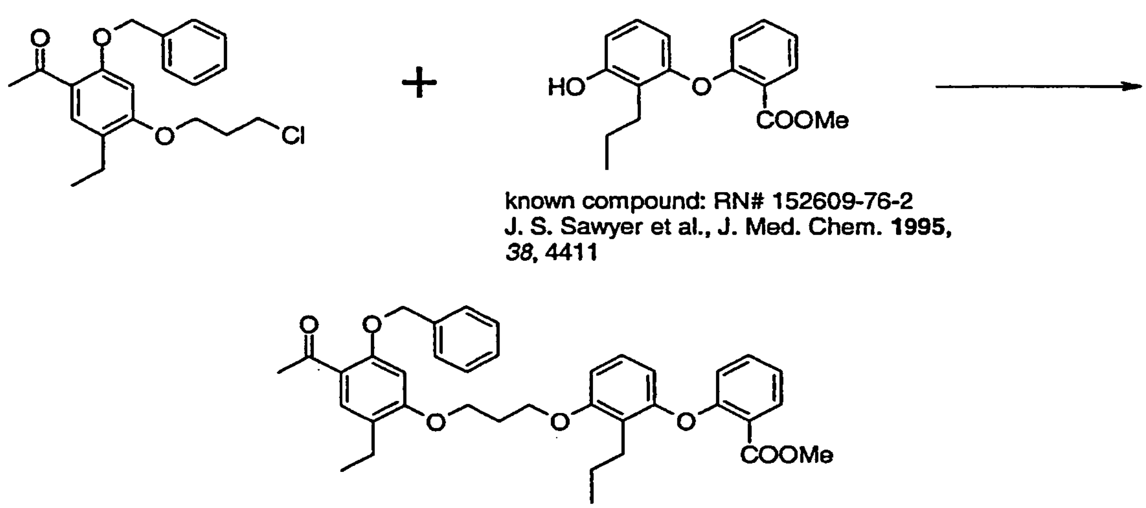
known compound: RN# 156005-61-7
R. W. Harper et al., J. Med. Chem. **1994**, *37(15)*, 2411-20

A. Preparation of 1-[2-benzyloxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone.

A mixture of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (26.1 g, 102 mmol), cesium carbonate (33.4 g, 103 mmol), and benzyl bromide (12.2 ml, 103 mmol), in N,N-dimethylformamide (300 mL) was stirred for 5 h at room temperature. The mixture was diluted with ethyl acetate and washed four times with water. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting oil was triturated with ethyl acetate and hexane, allowed to stand for 18 h, then cooled at 0 °C for 3 h. The resulting precipitate was collected via vacuum filtration to provide 24.3 g (69%) of the title compound as white crystals: mp 60-61 °C. ^{1}H NMR ($CDCl_3$) δ 7.68 (s,

1H), 7.40 (m, 5H), 6.48 (s, 1H), 5.17 (s, 2H), 4.13 (t, J = 6 Hz, 2H), 3.75 (t, J = 6 Hz, 2H), 2.56 (s, 3H), 2.55 (q, J = 7 Hz, 2H), 2.26 (quintet, J = 6 Hz, 2H), 1.16 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{20}H_{24}ClO_3$ (p+1): m/z = 347.1414. Found: 347.1402; IR ($CHCl_3$, cm^{-1}) 1659, 1602, 1266.

Anal. Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.68. Found: C, 69.30; H, 6.52.

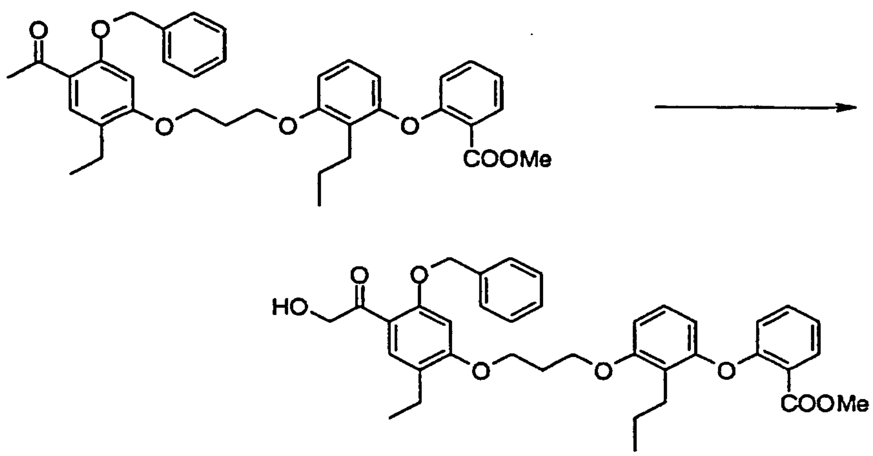


B. Preparation of 2-{3-[3-(4-acetyl-5-benzyloxy-2-ethylphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester.

A mixture of 1-[2-benzyloxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (7.27 g, 21.0 mmol) and sodium iodide (3.14 g, 23.1 mmol) in 2-butanone (100 mL) was heated at reflux for 18 h. The mixture was cooled to room

temperature, filtered, and concentrated in vacuo. The residue was dissolved in N,N-dimethylformamide (100 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (6.0 g, 21 mmol) and potassium carbonate (3.2 g, 23 mmol) at room temperature for 15 h. The mixture was diluted with ethyl acetate and washed four times with water and once with saturated sodium chloride solution. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 9.2 g (72%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 9 Hz, 1H), 7.69 (s, 1H), 7.38 (m, 6H), 7.12 (d, J = 8 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.50 (s, 1H), 6.44 (d, J = 9 Hz, 1H), 5.14 (s, 2H), 4.20 (m, 4H), 3.83 (s, 3H), 2.65 (t, J = 7 Hz, 2H), 2.57 (q, J = 7 Hz, 2H), 2.56 (s, 3H), 2.32 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 7 Hz, 2H), 1.15 (t, J = 8 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); IR ($CHCl_3$, cm^{-1}) 2965, 1726, 1602, 1461.

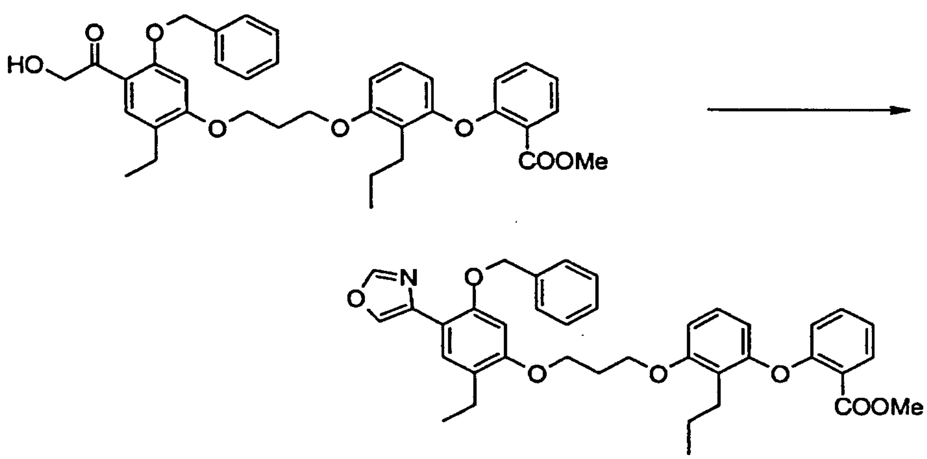
Anal. Calcd for $C_{37}H_{40}O_7$: C, 74.48; H, 6.76. Found: C, 74.39; H, 6.77.



C. Preparation of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(2-hydroxyacetyl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A mixture of 2-{3-[3-(4-acetyl-5-benzyloxy-2-ethylphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester (5.31 g, 8.89 mmol) and water (10 mL) in acetonitrile (50 mL) was treated with trifluoroacetic acid (1.4 mL), 18 mmol) and [bis(trifluoroacetoxy)iodo]benzene (7.65 g, 17.8 mmol). The resulting mixture was heated at reflux for 4 h then concentrated in vacuo. The residue was dissolved in methylene chloride and washed once with water. The aqueous layer was extracted twice with fresh portions of methylene chloride. The combined organic layers were washed three times with saturated sodium bicarbonate solution, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 20% ethyl acetate/80% hexane) of the residue provided 1.68 g (31%) of the title compound as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.88 (d, J = 9 Hz, 1H), 7.40 (m,

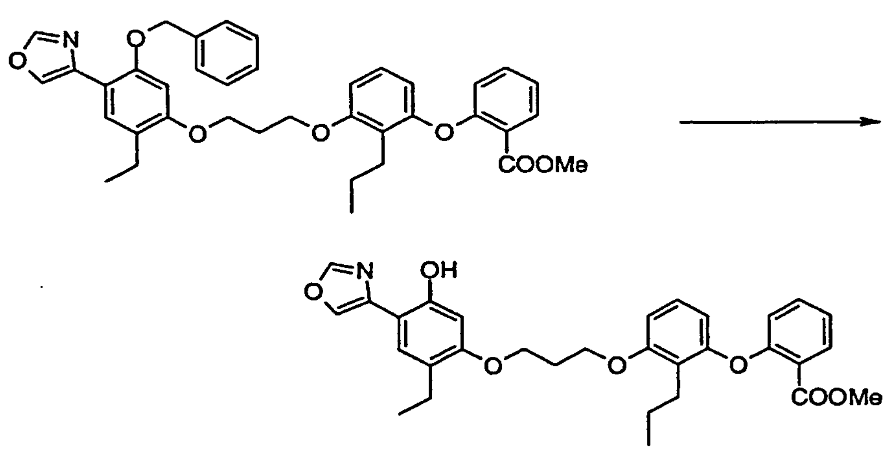
6H), 7.12 (d, J = 9 Hz, 1H), 7.05 (d, J = 9 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.50 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.15 (s, 2H), 4.65 (s, 2H), 4.22 (m, 4H), 3.83 (s, 3H), 2.65 (m, 4H), 2.34 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 7 Hz, 2H), 1.17 (t, J = 8 Hz, 3H), 0.89 (t, J = 8 Hz, 3H); TOS MS ES^+ exact mass calculated for $C_{37}H_{41}O_8$ (p+1): m/z = 613.2801. Found: 613.2833.



D. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-oxazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

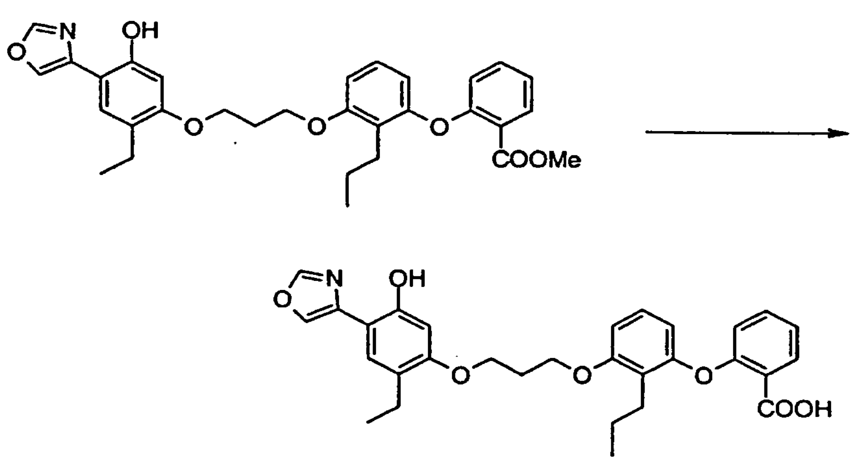
To a solution of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(2-hydroxyacetyl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (1.39 g, 2.27 mmol) in methylene chloride (20 mL) cooled to -78 °C was added triflic anhydride (0.57 mL, 3.4 mmol) and 2,6-lutidine (0.40 mL, 3.4 mmol). The resulting mixture was stirred for 1 h then poured into ether and water. The organic layer was separated and washed once with saturated sodium chloride solution, dried (sodium

sulfate), filtered, and concentrated in vacuo. The residue was dissolved in a 2:1 mixture of formamide/N,N-dimethylformamide (9 mL) and heated at 120 °C in a sealed tube for 4 h. The mixture was cooled to room temperature and diluted with ethyl acetate. The mixture was washed four times with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 89 mg (6%) of the title product as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.85 (s, 1H), 7.83 (m, 2H), 7.35 (m, 6H), 7.03 (d, J = 8 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 6.62 (d, J = 8 Hz, 1H), 6.52 (s, 1H), 6.35 (d, J = 8 Hz, 1H), 5.07 (s, 2H), 4.14 (m, 4H), 3.76 (s, 3H), 2.61 (m, 4H), 2.26 (quintet, J = 6 Hz, 2H), 1.48 (hextet, J = 7 Hz, 2H), 1.15 (t, J = 8 Hz, 3H), 0.84 (t, J = 8 Hz, 3H).



E. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-oxazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

To a solution of 2-{3-[3-(5-benzyloxy-2-ethyl-4-oxazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (89 mg, 0.14 mmol) in ethanethiol (2 mL) was treated with boron trifluoride etherate (0.27 mL, 2.2 mmol) at room temperature for 4 h. The solution was poured into ether and washed once with water, once with saturated sodium bicarbonate solution, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 15% ethyl acetate/85% hexane) of the residue provided 34 mg (45%) of the title product as a light brown oil. ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 1 Hz, 1H), 7.90 (d, J = 1 Hz, 1H), 7.88 (dd, J = 8, 2 Hz, 1H), 7.38 (t, J = 7 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 9 Hz, 1H), 7.06 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 6.70 (d, J = 9 Hz, 1H), 6.52 (s, 1H), 6.44 (d, J = 9 Hz, 1H), 4.20 (m, 4H), 3.83 (s, 3H), 2.65 (t, J = 8 Hz, 2H), 2.58 (q, J = 8 Hz, 2H), 2.33 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 7 Hz, 2H), 1.17 (t, J = 8 Hz, 3H), 0.91 (t, J = 8 Hz, 3H); MS ES+ m/e = 532 (p + 1).



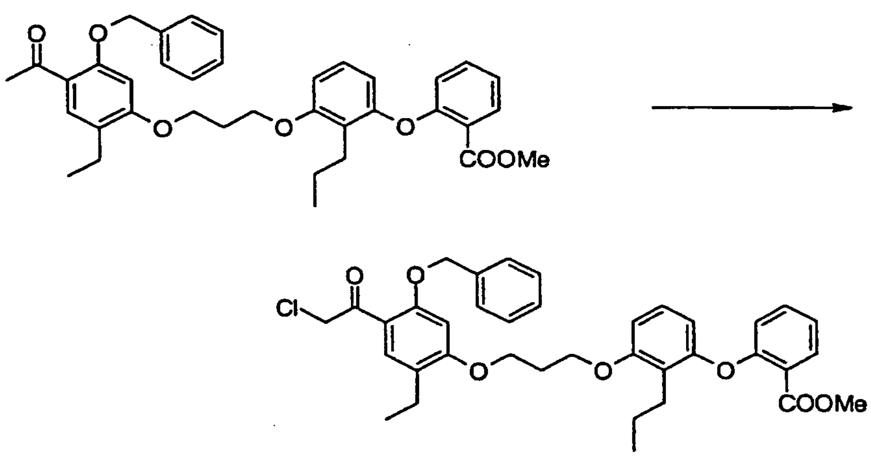
F. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-oxazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid.

To a solution of 2-{3-[3-(2-ethyl-5-hydroxy-4-oxazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (89 mg, 0.14 mmol) in methanol (2 mL) was added 1 M lithium hydroxide solution (0.28 mL) and the resulting mixture warmed at 60 °C for 3.5 h. The mixture was cooled to room temperature and concentrated in vacuo. The aqueous residue was diluted with water and the pH adjusted to ~4. The mixture was extracted three times with methylene chloride. The combined organic extracts were dried (sodium sulfate), filtered, and concentrated in vacuo to provide 27 mg (92%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 12.83 (bs, 1H), 10.12 (bs, 1H), 8.39 (s, 1H), 8.25 (s, 1H), 7.78 (dd, J = 8, 1 Hz, 1H), 7.64 (s, 1H), 7.47 (t, J = 8 Hz, 1H), 7.16 (m, 2H), 6.80 (t, J = 8 Hz, 2H), 6.56 (s, 1H), 6.35 (d, J = 8 Hz, 1H), 4.20 (t, J = 6 Hz, 2H), 4.12 (t, J = 6 Hz, 2H); 2.54 (m, 4H), 2.24 (quintet, J = 6 Hz, 2H), 1.43 (hextet, J = 8 Hz, 2H), 1.10 (t, J = 8 Hz, 3H), 0.80 (t, J = 8 Hz, 3H); TOF MS ES$^+$ exact mass calculated for $C_{30}H_{32}NO_7$ (p+1): m/z = 518.2179. Found: 518.2206; IR (KBr, cm^{-1}) 2961, 1696, 1460, 1222.

Anal. Calcd for $C_{30}H_{31}NO_7$: C, 69.62; H, 6.04; N, 2.71. Found: C, 68.71; H, 5.82; N, 2.65.

Example 2

Preparation of 2-(3-{3-[2-Ethyl-5-hydroxy-4-(3*H*-imidazol-4-yl)phenoxy]propoxy}-2-propyl-phenoxy)benzoic acid hydrochloride.

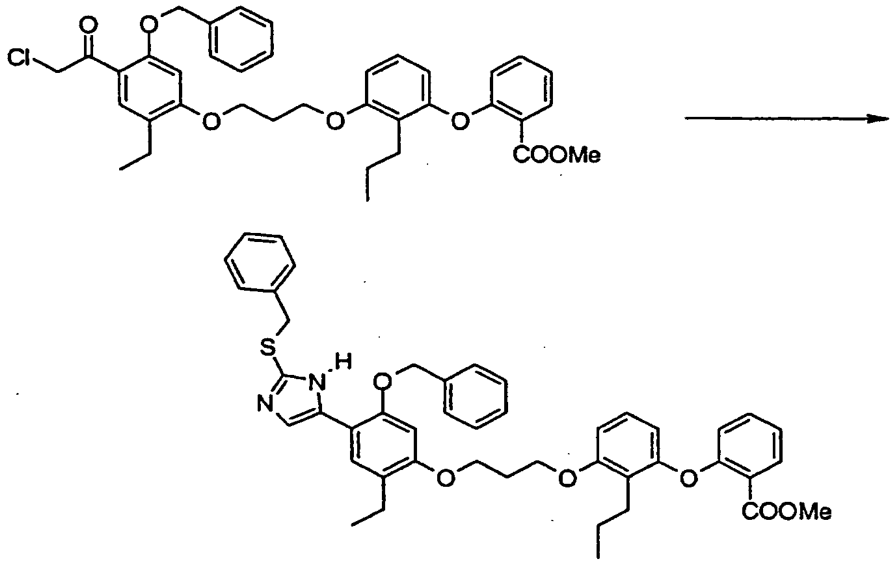


A. Preparation of 2-(3-{3-[5-benzyloxy-4-(2-chloroacetyl)-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

To a solution of 2-{3-[3-(4-acetyl-5-benzyloxy-2-ethylphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester (3.04 g, 5.09 mmol) in tetrahydrofuran (50 mL) cooled to -78 °C was added a solution of 1 M lithium hexamethyldisilazide in tetrahydrofuran (11.2 mL, 11.2 mmol) portion wise. After stirring for 20 min, trimethylsilyl chloride (2.6 mL, 20 mmol) was added and the mixture warmed to 0 °C and stirred for 30 min. The mixture was evaporated in vacuo and the residue dissolved in hexane. The resulting solution was filtered and concentrated in vacuo. The residue was dissolved in tetrahydrofuran (50 mL), cooled to 0 °C, and treated with N-chlorosuccinimide (750 mg, 5.6

mmol). The mixture was warmed to room temperature and stirred for 30 min, then heated at reflux for 2 h. The mixture was cooled to room temperature and treated with water (4 mL) and a solution of 1 N tetra-n-butylammonium fluoride in tetrahydrofuran (6 mL). After stirring for 15 min the mixture was diluted in ether and washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 1.94 g (60%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 7.89 (d, J = 8 Hz, 1H), 7.77 (s, 1H), 7.40 (m, 6H), 7.12 (d, J = 9 Hz, 1H), 7.06 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.49 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.15 (s, 2H), 4.68 (s, 2H), 4.20 (q, J = 6 Hz, 4H), 3.82 (s, 3H), 2.65 (t, J = 7 Hz, 2H), 2.59 (q, J = 7 Hz, 2H), 2.32 (quintet, J = 6 Hz, 2H), 1.54 (hextet, J = 8 Hz, 2H), 1.16 (t, J = 8 Hz, 3H), 0.89 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{37}H_{40}ClO_7$ (p+1): m/z = 631.2463. Found: 631.2470; IR ($CHCl_3$, cm^{-1}) 2964, 1720, 1603, 1461.

Anal. Calcd for $C_{37}H_{39}ClO_7$: C, 70.41; H, 6.23. Found: C, 70.04; H, 5.97.

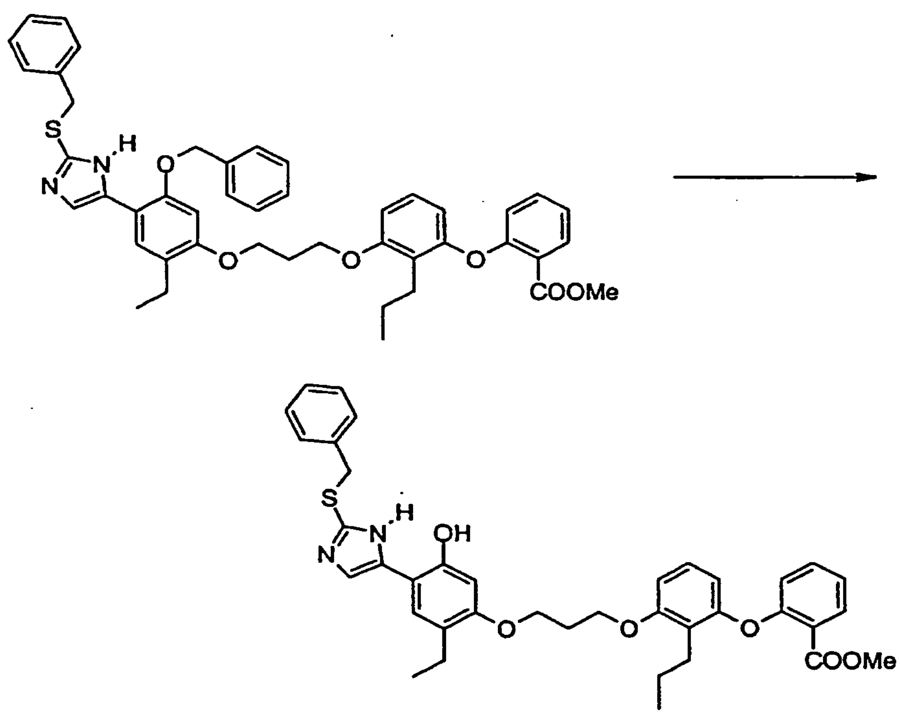


B. Preparation of 2-(3-{3-[5-benzyloxy-4-(2-benzylsulfanyl-3*H*-imidazol-4-yl)-2-ethyl-phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A mixture of 2-(3-{3-[5-benzyloxy-4-(2-chloroacetyl)-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (800 mg, 1.27 mmol), 2-benzyl-2-thiopseudourea hydrochloride (313 mg, 1.52 mmol), sodium iodide (77 mg, 0.51 mmol), and potassium carbonate (700 mg, 5.06 mmol) in N,N-dimethylformamide (20 mL) was treated at 80 °C for 6 h. The mixture was cooled, diluted with diethyl ether, and washed once with water. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 30% ethyl acetate/70% hexane) of the residue provided 376 mg (40%) of the title compound as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8 Hz, 1H), 7.36 (m, 9H), 7.20 (m, 5H), 7.21 (d, J = 9 Hz, 1H), 7.06 (d, J = 8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.67 (d, J =

8 Hz, 1H), 6.55 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.07 (s, 2H), 4.21 (t, J = 6 Hz, 2H), 4.18 (t, J = 6 Hz, 2H), 4.10 (s, 2H), 3.83 (s, 3H), 2.63 (m, 4H), 2.31 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 7 Hz, 2H), 1.18 (t, J = 8 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{45}H_{47}N_2O_6S$ (p+1): m/z = 743.3155. Found: 743.3142; IR ($CHCl_3$, cm^{-1}) 2963, 1720, 1602, 1453.

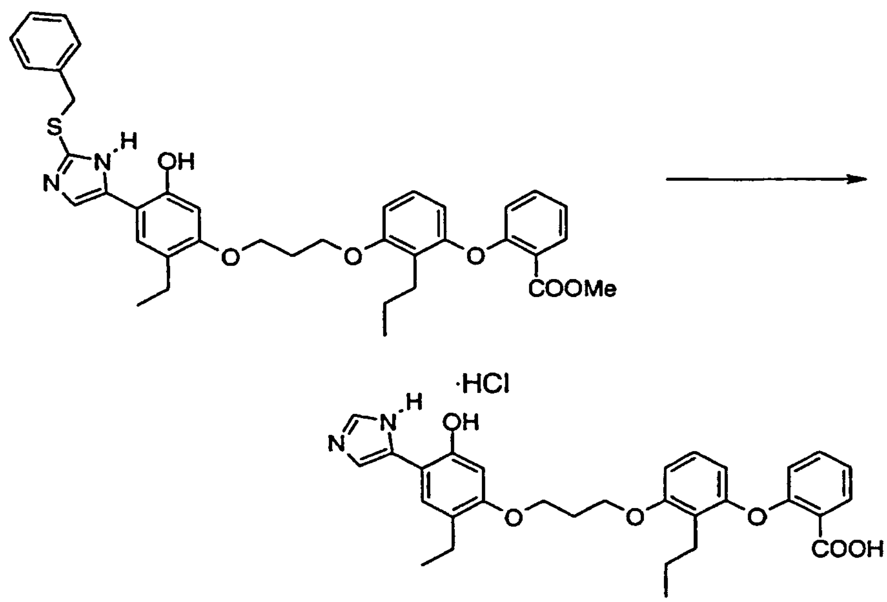
Anal. Calcd for $C_{45}H_{46}N_2O_6S$: C, 72.75; H, 6.24; N, 3.77. Found: C, 72.69; H, 6.17; N, 3.56.



C. Preparation of 2-(3-{3-[4-(2-benzylsulfanyl-3*H*-imidazol-4-yl)-2-ethyl-5-hydroxyphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A solution of 2-(3-{3-[5-benzyloxy-4-(2-benzylsulfanyl-3*H*-imidazol-4-yl)-2-ethyl-phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (360 mg, 0.49 mmol) in ethanethiol (7 mL) was treated with boron trifluoride etherate at room temperature for 3.5 h. The mixture was diluted with diethyl ether and water. The organic layer was separated and washed with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 20% ethyl acetate/80% hexane) of the residue provided 154 mg (48%) of the title compound as an orange oil. ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8 Hz, 1H), 7.36 (t, J = 7 Hz, 1H), 7.20 (m, 7H), 7.12 (s, 1H), 7.05 (m, 3H), 6.79 (d, J = 8 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.54 (s, 1H), 6.41 (d, J = 8 Hz, 1H), 4.20 (s, 2H), 4.17 (m, 4H), 3.82 (s, 3H), 2.62 (t, J = 8 Hz, 2H), 2.54 (q, J = 7 Hz, 2H), 2.30 (quintet, J = 6 Hz, 2H), 1.53 (hextet, J = 8 Hz, 2H), 1.14 (t, J = 7 Hz, 3H), 0.89 (t, J = 8 Hz, 3H); TOF MS ES^{+} exact mass calculated for $C_{38}H_{41}N_2O_6S$ (p+1): m/z = 653.2685. Found: 653.2669.

Anal. Calcd for $C_{38}H_{40}N_2O_6S$: C, 69.92; H, 6.18; N, 4.29. Found: C, 69.44; H, 6.25; N, 3.99.



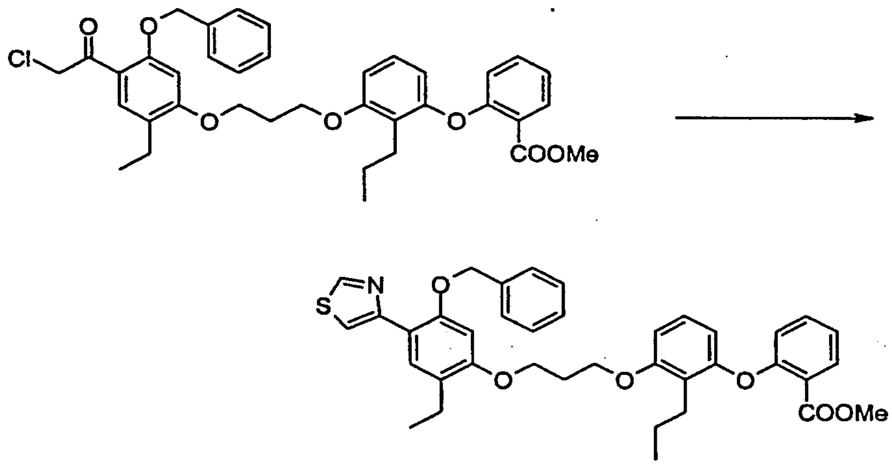
D. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(3H-imidazol-4-yl)phenoxy]propoxy}-2-propyl-phenoxy)benzoic acid hydrochloride.

A solution of 2-(3-{3-[4-(2-benzylsulfanyl-3*H*-imidazol-4-yl)-2-ethyl-5-hydroxyphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (154 mg, 0.235 mmol) in methanol (3 mL) was treated with 1 N lithium hydroxide solution at 60 °C for 3.5 h. The mixture was cooled to room temperature and concentrated in vacuo. The solution was diluted with water and adjusted to pH 4. The aqueous solution was extracted three times with methylene chloride. The combined organic layers were dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in ethanol (3 mL) and treated with 0.2 N sodium hydroxide solution (1 mL) and Raney nickel (75 mg) at 75 °C for 4 h. The mixture was cooled to room temperature,

filtered through Celite™, and the filtrate concentrated in vacuo. The residue was diluted with water and adjusted to pH 2 with 1 N hydrochloric acid. The resulting precipitate was collected via vacuum filtration to provide 27 mg (21%) of the title compound. TOF MS ES$^+$ exact mass calculated for $C_{30}H_{33}N_2O_6$ (p+1): m/z = 517.2339. Found: 517.2340.

Example 3

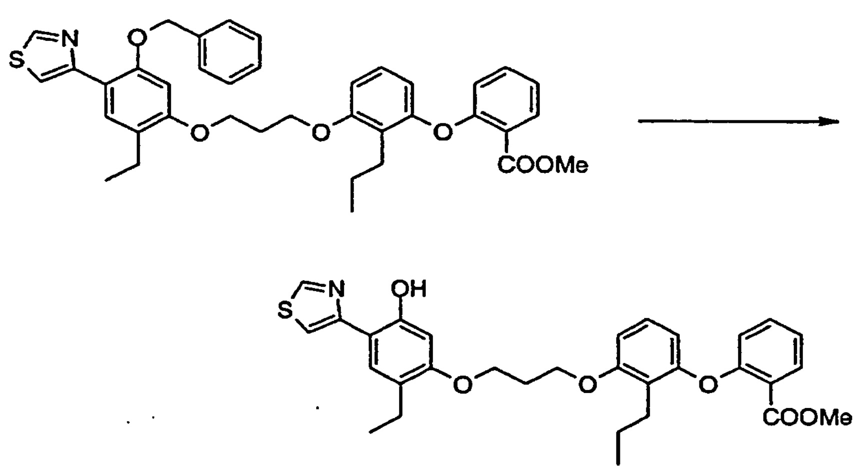
Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-thiazol-4-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid.



A. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-thiazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

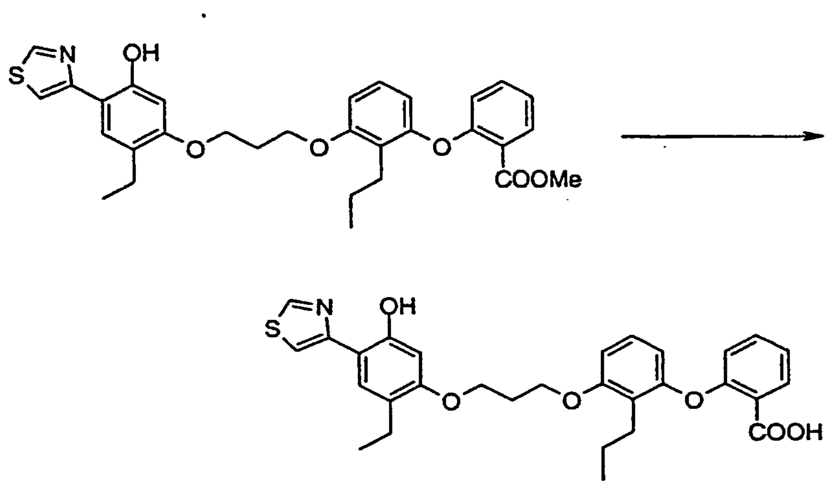
A mixture of 2-(3-{3-[5-benzyloxy-4-(2-chloroacetyl)-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (500 mg, 0.792 mmol), thioformamide (20 mL, 8.0 mmol), and magnesium carbonate in dioxane (10 mL) was heated at reflux for 2 h. The mixture was cooled to room temperature

and diluted with diethyl ether and 0.2 M sodium hydroxide solution. The organic layer was separated, washed with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 254 mg (50%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1H), 8.11 (s, 1H), 7.87 (dd, J = 8, 1 Hz, 1H), 7.84 (d, J = 1 Hz, 1H), 7.40 (m, 6H), 7.08 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.62 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.16 (s, 2H), 4.21 (t, J = 6 Hz, 4H), 3.83 (s, 3H), 2.68 (m, 4H), 2.32 (quintet, J = 6 Hz, 2H), 1.56 (hextet, J = 8 Hz, 2H), 1.21 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{38}H_{40}NO_6S$ (p+1): m/z = 638.2576. Found: 638.2579. IR ($CHCl_3$, cm^{-1}) 2964, 1719, 1563, 1461.



B. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A solution of 2-{3-[3-(5-benzyloxy-2-ethyl-4-thiazol-4-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester (243 mg, 0.366 mmol) in ethanethiol (7 mL) was treated with boron trifluoride etherate at room temperature for 4 h. The mixture was diluted with diethyl ether, washed once with water, once with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 15% ethyl acetate/85% hexane) of the residue provided 131 mg (65%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.88 (d, J = 1 Hz, 1H), 7.88 (dd, J = 8, 1 Hz, 1H), 7.44 (d, J = 1 Hz, 1H), 7.38 (m, 2H), 7.08 (m, 2H), 6.81 (d, J = 8 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.55 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 4.21 (t, J = 6 Hz, 4H), 3.83 (s, 3H), 2.63 (m, 4H), 2.33 (quintet, J = 6 Hz, 2H), 1.56 (hextet, J = 8 Hz, 2H), 1.19 (t, J = 8 Hz, 3H), 0.91 (t, J = 7 Hz, 3H); TOF MS ES^{+} exact mass calculated for $C_{31}H_{34}NO_6S$ (p+1): m/z = 548.2107. Found: 548.2085.



C. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid.

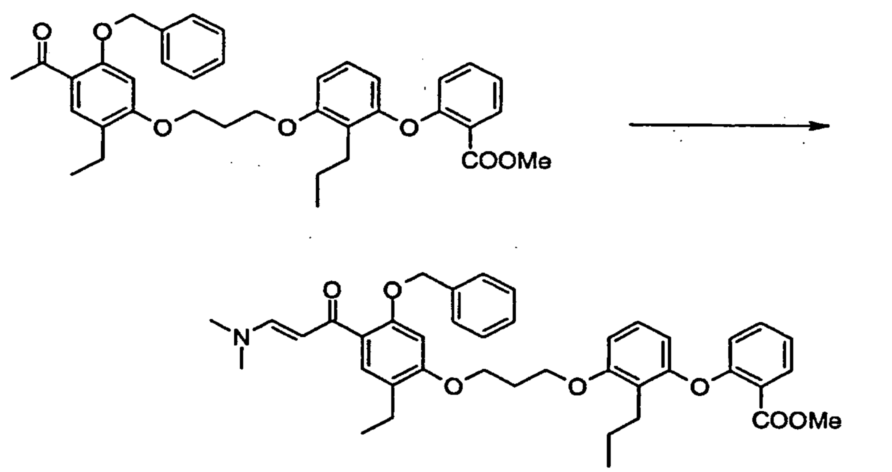
A solution of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiazol-4-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (130 mg, 0.236 mmol) in methanol (4 mL) was treated with 1 M lithium hydroxide solution at 60 °C for 3 h. The mixture was cooled to room temperature, concentrated in vacuo, and diluted with water. The solution was adjusted to pH ~4 and extracted three times with methylene chloride. The combined organic layers were dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in a minimum of methylene chloride and hexane was added until the solution became cloudy. The mixture was concentrated slowly in vacuo to give 96 mg (76%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.23 (dd, J = 8, 1 Hz, 1H), 7.41 (m, 2H), 7.38 (s, 1H), 7.29 (m, 2H), 6.82 (d, J = 8 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 6.62 (d, J = 8 Hz, 1H), 6.54 (s, 1H), 4.25 (t, J = 6 Hz, 2H), 4.22 (t, J = 6 Hz, 2H), 2.59

(m, 4H), 2.35 (quintet, J = 6 Hz, 2H), 1.50 (hextet, J = 8 Hz, 2H), 1.19 (t, J = 7 Hz, 3H), 0.88 (t, J = 8 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{30}H_{32}NO_6S$ (p+1): m/z = 534.1950. Found: 534.1957. IR ($CHCl_3$, cm^{-1}) 2965, 1738, 1454.

Anal. Calcd for $C_{30}H_{31}NO_6S$: C, 67.52; H, 5.86; N, 2.62. Found: C, 67.19; H, 5.72; N, 2.53.

Example 4

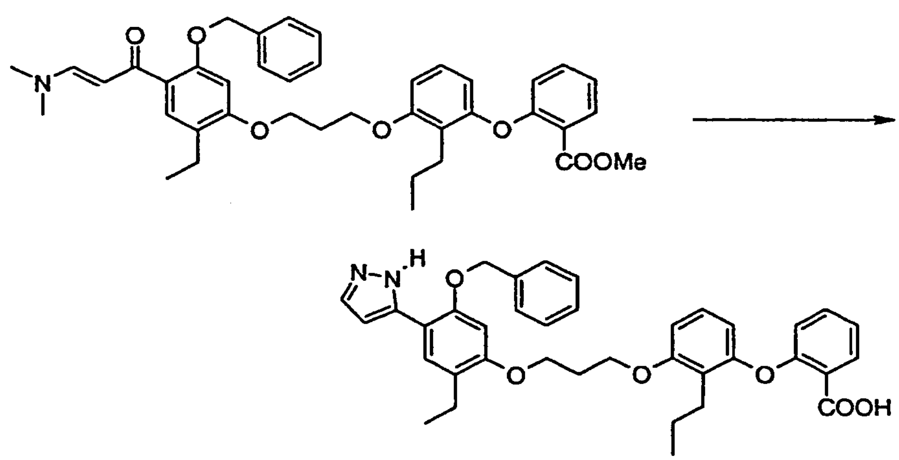
Preparation of 2-(3-{3-[2-Ethyl-5-hydroxy-4-(2*H*-pyrazol-3-yl)phenoxy]propoxy}-2-propyl-phenoxy)benzoic acid.



A. Preparation of 2-(3-{3-[5-benzyloxy-4-(3-dimethylaminoacryloyl)-2-ethyl-phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

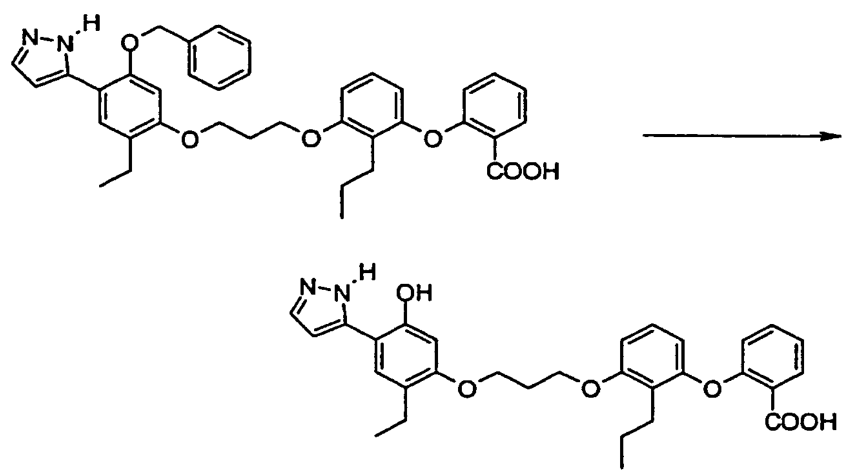
A mixture of 2-(3-{3-[4-acetyl-5-benzyloxy-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (3.07 g, 5.04 mmol) and dimethylformamide dimethylacetal (0.9 mL, 7 mmol) in N,N-dimethylformamide (3 mL) was heated at 110-120 °C for 35 h. The mixture was cooled to room temperature and diluted with a mixture of ethyl acetate and 1 N hydrochloric acid. The organic layer was separated, washed twice with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 30% ethyl acetate/70% hexane to ethyl acetate) of the residue provided 2.1 g (63%) of the title compound as a yellow oil. TOF MS ES^+ exact mass calculated for $C_{40}H_{46}NO_7$ (p+1): m/z = 652.3274. Found: 652.3270. IR ($CHCl_3$, cm^{-1}) 2965, 1720, 1605.

Anal. Calcd for $C_{40}H_{45}NO_7$: C, 73.71; H, 6.96; N, 2.15. Found: C, 73.72; H, 6.95; N, 2.18.



B. Preparation of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(2*H*-pyrazol-3-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid. A solution of 2-(3-{3-[5-benzyloxy-4-(3-dimethylaminoacryloyl)-2-ethyl-phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (550 mg, 0.843 mmol in methanol (30 mL) was treated with 1 M lithium hydroxide solution at 60 °C for 3 h. The mixture was cooled to room temperature and diluted with ethyl acetate and 0.5 M hydrochloric acid. The organic layer was separated, washed with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in methanol (15 mL) and treated with water (4 mL) and hydrazine monohydrate (0.50 mL, 7.7 mmol) at reflux for 3 h. The mixture was diluted with ethyl acetate and 1 N hydrochloric acid. The organic layer was separated, washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and concentrated in vacuo. Chromatography (30% ethyl acetate/69% hexane/1% acetic acid) of the residue provided 350 mg (65%) of the title compound as the acetate salt. A portion of this material was free-based with sodium bicarbonate to provide an analytical sample. ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, J = 8, 2 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.38 (m, 5H), 7.15 (m, 2H), 6.78 (d, J = 8 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.61 (d, J = 8 Hz, 1H), 6.58 (s, 1H), 6.55 (bs, 1H), 5.18 (s, 2H), 4.22 (t, J = 6 Hz, 2H), 4.17 (t, J = 6 Hz, 2H), 2.58 (m, 4H), 2.30 (quintet, J = 6 Hz, 2H), 1.47 (hextet, J = 8 Hz, 2H), 1.18 (t, J = 7 Hz, 3H), 0.88 (t, J = 8 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{37}H_{39}N_2O_6$ (p+1): m/z = 607.2808. Found: 607.2831. IR ($CHCl_3$, cm^{-1}) 2965, 1739, 1604, 1454.

Anal. Calcd for $C_{37}H_{38}N_2O_6$: C, 73.25; H, 6.31; N, 4.62. Found: C, 73.31; H, 6.30; N, 4.62.



C. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(2*H*-pyrazol-3-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid.

A solution of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(2*H*-pyrazol-3-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid (300 mg, 0.490 mmol) in ethanethiol (2.5 mL) was treated with boron trifluoride etherate (2 mL) at room temperature for 3 h, at which time an additional portion of boron trifluoride etherate (1 mL) was added and stirring resumed for an additional 1 h. The mixture was diluted with diethyl ether and water. The organic layer was separated, washed with water, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 15% ethyl acetate/85% hexane to 60% ethyl acetate/40% hexane) of the residue provided 60 mg (24%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 8 Hz, 1H), 7.61 (s, 1H), 7.42 (t, J = 7 Hz, 1H), 7.30 (s, 1H), 7.19 (d, J = 8 Hz, 1H),

7.15 (d, J = 8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 6.61 (s, 1H), 6.60 (d, J = 8 Hz, 1H), 6.54 (s, 1H), 4.20 (m, 4H), 2.58 (m, 4H), 2.33 (quintet, J = 6 Hz, 2H), 1.48 (hextet, J = 8 Hz, 2H), 1.17 (t, J = 8 Hz, 3H), 0.86 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{30}H_{33}N_2O_6$ (p+1): m/z = 517.2339. Found: 517.2334.

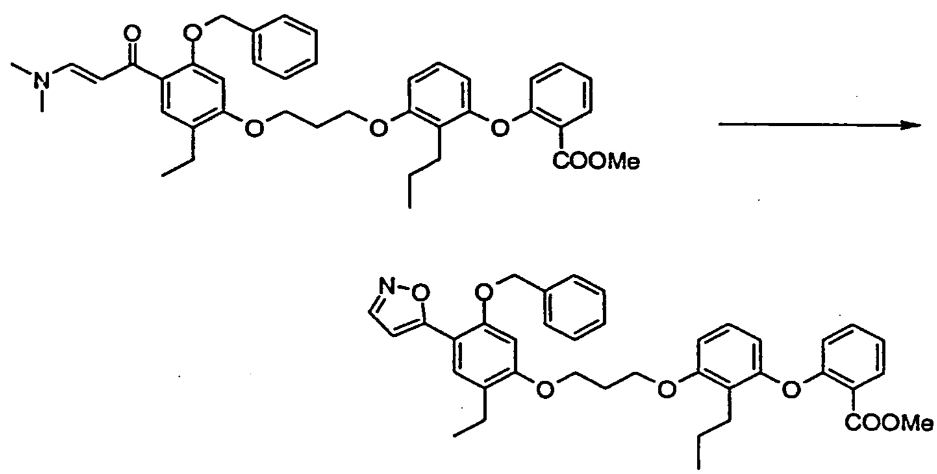
IR ($CHCl_3$, cm^{-1}) 2965, 1738, 1454.

Anal. Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42.

Found: C, 69.73; H, 6.33; N, 5.25.

Example 5

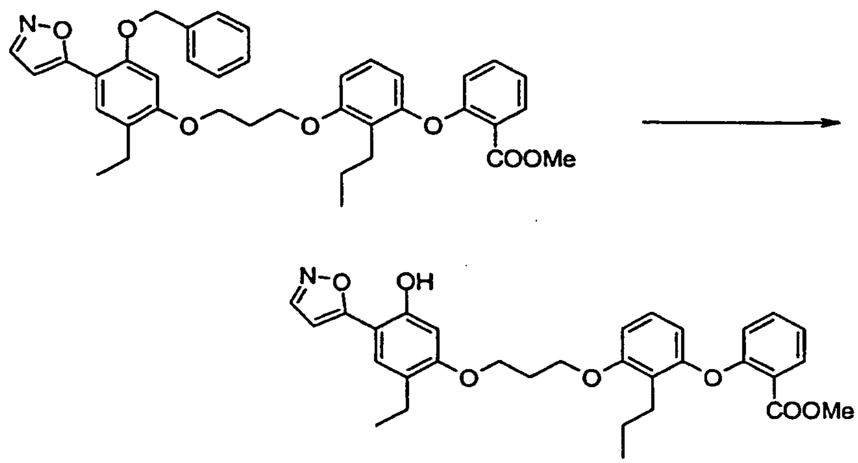
Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-isoxazol-5-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid.



A. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-isoxazol-5-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A mixture of 2-(3-{3-[5-benzyloxy-4-(3-dimethylaminoacryloyl)-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (280 mg, 0.43 mmol), hydroxylamine hydrochloride (75 mg, 1.1 mmol), and water (1 mL) in methanol (4 mL) was heated at reflux for 2 h. The mixture was cooled to room temperature and diluted with diethyl ether and water. The organic layer was separated, washed with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 202 mg (76%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 2 Hz, 1H), 7.88 (dd, J = 9, 2 Hz, 1H), 7.79 (s, 1H), 7.40 (m, 7H), 7.08 (m, 2H), 6.68 (d, J = 8 Hz, 1H), 6.59 (s, 1H), 6.58 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.15 (s, 2H), 4.21 (t, J = 6 Hz, 4H), 3.82 (s, 3H), 2.65 (m, 4H), 2.33 (quintet, J = 6 Hz, 2H), 1.56 (hextet, J = 8 Hz, 2H), 1.20 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES$^+$ exact mass calculated for $C_{38}H_{40}NO_7$ (p+1): m/z = 622.2805. Found: 622.2817. IR ($CHCl_3$, cm^{-1}) 2964, 1720, 1461.

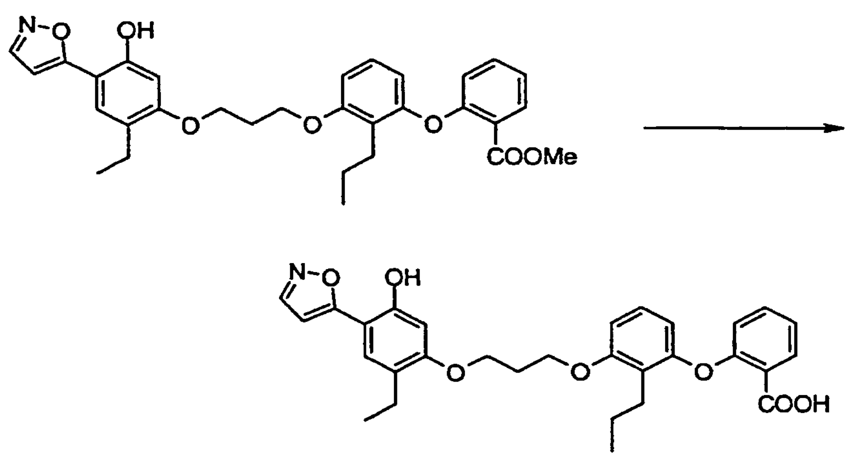
Anal. Calcd for $C_{38}H_{39}NO_7$: C, 73.41; H, 6.32; N, 2.25. Found: C, 73.20; H, 6.34; N, 2.27.



B. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-isoxazol-5-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A solution of 2-{3-[3-(5-benzyloxy-2-ethyl-4-isoxazol-5-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (180 mg, 0.289 mmol) in ethanethiol (5 mL) was treated with boron trifluoride etherate (1.5 mL) at room temperature for 2 h, at which time an additional portion of boron trifluoride etherate (0.5 mL) was added and stirring resumed for an additional 1 h. The mixture was diluted with diethyl ether and water. The organic layer was separated, washed once with saturated sodium bicarbonate solution, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 15% ethyl acetate/85% hexane) of the residue provided 94 mg (61%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 8.28 (d, J = 1 Hz, 1H), 7.88 (dd, J = 8, 2 Hz, 1H), 7.38 (t, J = 8 Hz,1H), 7.36 (s, 1H), 7.08 (t, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 6.67

(d, J = 8 Hz, 1H), 6.50 (s, 1H), 6.45 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 4.20 (m, 4H), 3.83 (s, 3H), 2.62 (m, 4H), 2.34 (quintet, J = 6 Hz, 2H), 1.54 (hextet, J = 8 Hz, 2H), 1.18 (t, J = 8 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES$^+$ exact mass calculated for $C_{31}H_{34}NO_7$ (p+1): m/z = 532.2335. Found: 532.2335. IR ($CHCl_3$, cm^{-1}) 2964, 1715, 1601, 1461. Anal. Calcd for $C_{31}H_{33}NO_7$: C, 70.04; H, 6.26; N, 2.63. Found: C, 70.13; H, 6.35; N, 2.63.



C. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-isoxazol-5-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid.

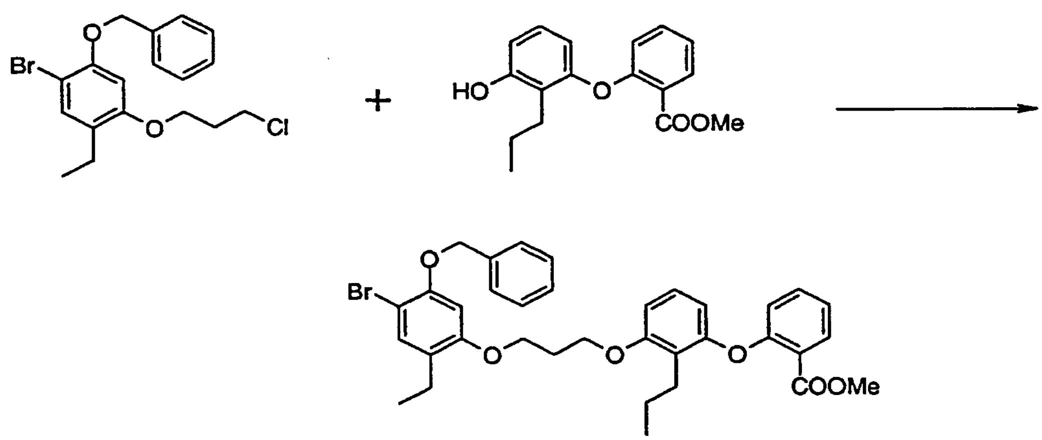
To a solution of 2-{3-[3-(2-ethyl-5-hydroxy-4-isoxazol-5-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (94 mg, 0.18 mmol) in methanol (3 mL) was added 1 M lithium hydroxide solution (1 mL) and the resulting mixture warmed at 60 °C for 3 h. The mixture was cooled to room temperature and concentrated in vacuo. The aqueous residue was diluted with water and the pH adjusted to ~4. The

mixture was extracted three times with methylene chloride. The combined organic extracts were dried (sodium sulfate), filtered, and concentrated in vacuo to provide 12 mg (13%) of the title compound as an off-white amorphous solid. ^1H NMR ($CDCl_3$) δ 8.26 (s, 1H), 8.20 (dd, J = 8, 1 Hz, 1H), 7.49 (t, J = 6 Hz, 1H), 7.36 (s, 1H), 7.18 (d, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.02 (bs, 1H), 6.80 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 6.60 (d, J = 8 Hz, 1H), 6.50 (s, 1H), 6.46 (s, 1H), 4.22 (t, J = 6 Hz, 2H), 4.19 (t, J = 6 Hz, 2H); 2.57 (m, 4H), 2.34 (quintet, J = 6 Hz, 2H), 1.47 (hextet, J = 8 Hz, 2H), 1.16 (t, J = 8 Hz, 3H), 0.85 (t, J = 7 Hz, 3H); TOS MS ES^+ exact mass calculated for $C_{30}H_{32}NO_7$ (p+1): m/z = 518.2179. Found: 518.2175.

Anal. Calcd for $C_{30}H_{31}NO_7$: C, 69.62; H, 6.04; N, 2.71. Found: C, 69.57; H, 6.15; N, 2.74.

Example 6

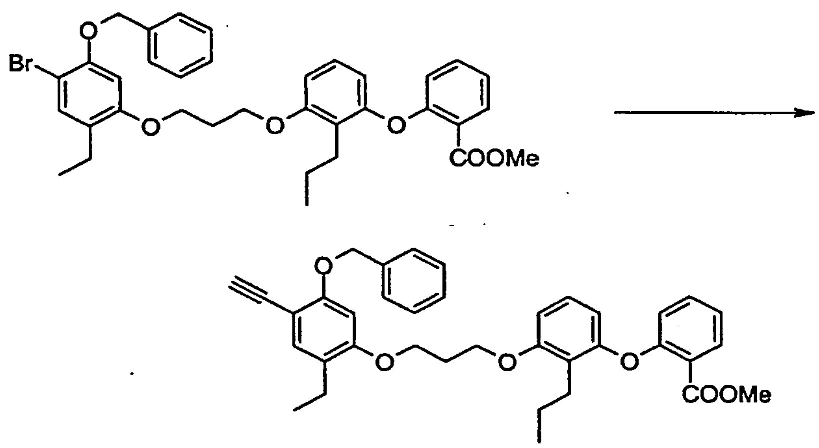
Preparation of 2-(3-{3-[2-Ethyl-5-hydroxy-4-(3*H*-[1,2,3]triazol-4-yl)phenoxy]propoxy}-2-propyl-phenoxy)benzoic acid.



A. Preparation of 2-{3-[3-(5-benzyloxy-4-bromo-2-ethylphenoxy)propoxy]-2-propylphenoxy}-benzoic acid methyl ester.

A mixture of 5-benzyloxy-4-bromo-1-(3-chloropropoxy)-2-ethylbenzene (1.19 g, 3.11 mmol), 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (0.89 g, 3.1 mmol), potassium carbonate (1.29 g, 9.34 mmol), potassium iodide (0.52 g, 3.1 mmol), and methyl sulfoxide (2 mL) in 2-butanone (20 mL) was heated at reflux for 48 h. The mixture was cooled to room temperature, diluted with diethyl ether, and washed once with water. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 6% ethyl acetate/94% hexane) of

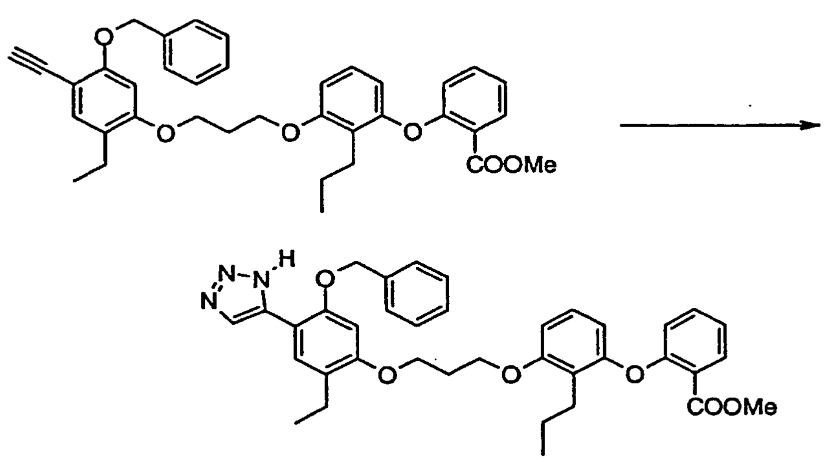
the residue provided 1.34 g (68%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.91 (dd, J = 8, 2 Hz, 1H), 7.50 (d, J = 7 Hz, 2H), 7.38 (m, 5H), 7.15 (d, J = 8 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 6.55 (s, 1H), 6.48 (, J = 8 Hz, 1H), 5.16 (s, 2H), 4.21 (t, J = 6 Hz, 2H), 4.15 (t, J = 6 Hz, 2H), 3.83 (s, 3H), 2.68 (t, J = 8 Hz, 2H), 2.58 (q, J = 7 Hz, 2H), 2.31 (quintet, J = 6 Hz, 2H), 1.58 (hextet, J = 6 Hz, 2H), 1.17 (t, J = 7 Hz, 3H), 0.93 (t, J = 7 Hz, 3H).



B. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-ethynylphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester.

A mixture of 2-{3-[3-(5-benzyloxy-4-bromo-2-ethylphenoxy)propoxy]-2-propylphenoxy}-benzoic acid methyl ester (1.50 g, 2.37 mmol), tri-n-butylethynyltin (0.82 mL, 2.8 mmol), and tetrakis(triphenylphosphine)palladium (0) (1.0 g, 0.95 mmol) in N,N-dimethylformamide (25 mL) was purged with argon and heated in a sealed tube at 120 °C for 24 h. The mixture was cooled to room temperature and

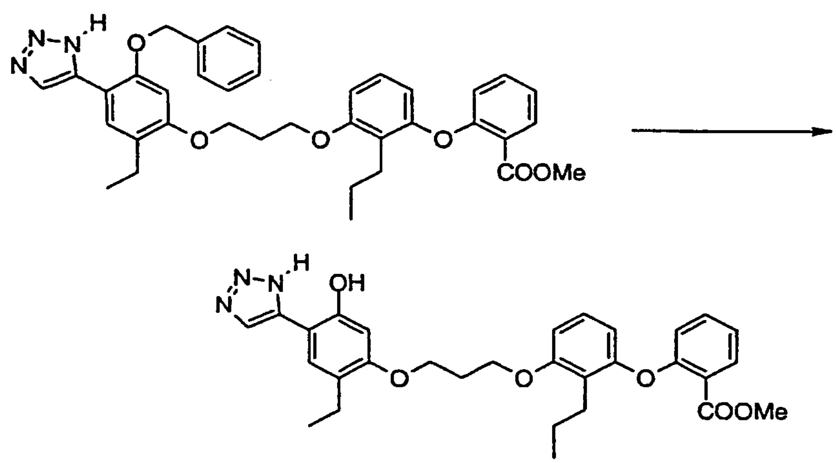
filtered. The filtrate was diluted with ethyl acetate, washed four times with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 532 mg (39%) of the title compound as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, J = 8, 2 Hz, 1H), 7.79 (s, 1H), 7.20-7.50 (m, 6H), 7.10 (d, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.43 (m, 2H), 5.16 (s, 2H), 4.17 (t, J = 6 Hz, 2H), 4.11 (t, J = 6 Hz, 2H), 3.83 (s, 3H), 3.23 (s, 1H), 2.64 (t, J = 8 Hz, 2H), 2.53 (q, J = 7 Hz, 2H), 2.27 (quintet, J = 6 Hz, 2H), 1.53 (m, 2H), 1.13 (t, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{37}H_{39}O_6$ (p+1): m/z = 579.2747. Found: 579.2739.



C. Preparation of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(3*H*-[1,2,3]triazol-4-yl)phenoxy]-propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A mixture of 2-{3-[3-(5-benzyloxy-2-ethyl-4-ethynylphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester (517 mg, 0.893 mmol) and trimethylsilyl azide (3.0 mL, 18 mmol) was heated in toluene (20 mL) in a sealed tube at 130 °C for 120 h. The mixture was cooled to room temperature and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane to 50% ethyl acetate/50% hexane) of the residue provided 347 mg (88% based upon recovered starting material) of the title compound as a brown solid. ^{1}H NMR ($CDCl_3$) δ 8.10 (bs, 1H), 7.89 (dd, J = 8, 2 Hz, 1H), 7.76 (s, 1H), 7.40 (m, 7H), 7.10 (d, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.62 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.18 (s, 2H), 4.21 (m, 4H), 3.82 (s, 3H), 2.65 (m, 4H), 2.32 (quintet, J = 6 Hz, 2H), 1.56 (hextet, J = 8 Hz, 2H), 1.21 (t, J = 8 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{37}H_{40}N_3O_6$ (p+1): m/z = 622.2917. Found: 622.2946. IR ($CHCl_3$, cm^{-1}) 3400, 1721, 1602, 1453.

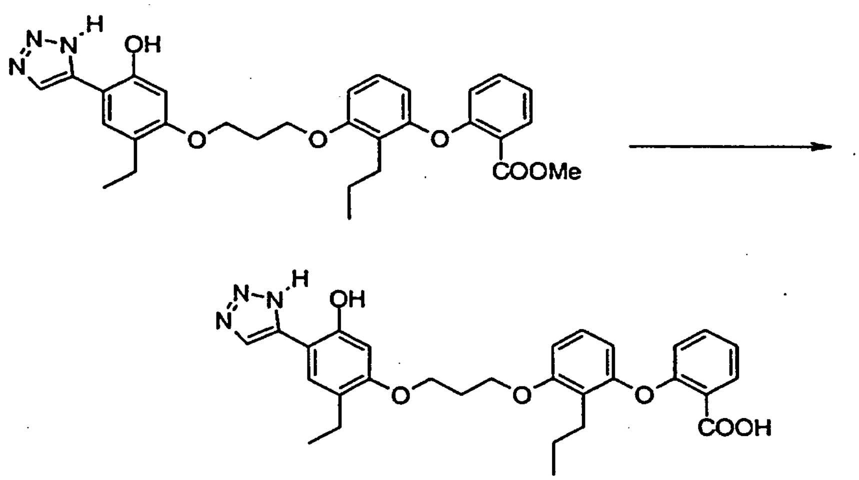
Anal. Calcd for $C_{37}H_{39}N_3O_6$: C, 71.48; H, 6.32; N, 6.76. Found: C, 70.28; H, 6.07; N, 6.54.



D. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(3*H*-[1,2,3]triazol-4-yl)phenoxy]-propoxy}-2-propyl-phenoxy)benzoic acid methyl ester.

A solution of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(3*H*-[1,2,3]triazol-4-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (330 mg, 0.531 mmol) in ethanethiol (9 mL) was treated with boron trifluoride etherate (2.0 mL,16 mmol) for 1 h at room temperature and then with an additional portion of boron trifluoride etherate (1.0 mL) for 1 h. The mixture was diluted with diethyl ether and water. The organic layer was washed once with saturated sodium bicarbonate solution, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 30% ethyl acetate/70% hexane to 50% ethyl acetate/50% hexane) of the residue provided 180 mg (63%) of the title compound as a brown solid. ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.88 (dd, J = 8, 2 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.31 (s, 1H), 7.10 (d, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.59 (s, 1H), 6.43 (d, J = 8 Hz,

1H), 4.20 (m, 4H), 3.83 (s, 3H), 2.63 (m, 4H), 2.34 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 8 Hz, 2H), 1.19 (t, J = 8 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{30}H_{34}N_3O_6$ (p+1): m/z = 532.2447. Found: 532.2466. IR ($CHCl_3$, cm^{-1}) 2964, 1718, 1453. Anal. Calcd for $C_{30}H_{33}N_3O_6$: C, 67.78; H, 6.26; N, 7.90. Found: C, 66.80; H, 6.02; N, 7.53.



E. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(3*H*-[1,2,3]triazol-4-yl)phenoxy]-propoxy}-2-propylphenoxy)benzoic acid.

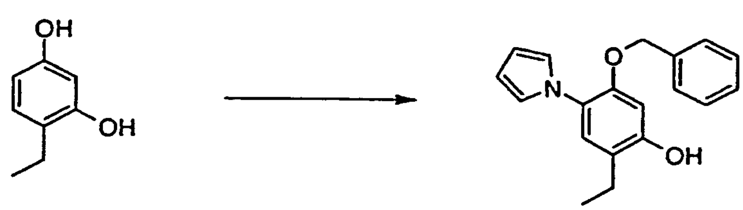
A solution of 2-(3-{3-[2-ethyl-5-hydroxy-4-(3*H*-[1,2,3]triazol-4-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (160 mg, 0.30 mmol) in methanol (5 mL) was treated 1 N lithium hydroxide solution (1.5 mL) at 60 °C for 3.5 h. The mixture was cooled to room temperature, diluted with water, and adjusted to ~pH 4. The resulting mixture was extracted three times with methylene chloride. The

combined organic extracts were dried (sodium sulfate), filtered, and concentrated in vacuo to provide 134 mg (86%) of the title compound as a tan solid. ^{1}H NMR (DMSO-d) δ 14.98 (bs, 1H), 12.80 (bs, 1H), 10.02 (bs, 1H), 8.17 (bs, 1H), 7.77 (dd, J = 7, 2 Hz, 1H), 7.60 (bs, 1H), 7.47 (t, J = 8 Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.57 (s, 1H), 6.35 (d, J = 8 Hz, 1H), 4.22 (t, J = 6 Hz, 2H), 4.15 (t, J = 6 Hz, 2H), 2.54 (m, 4H), 2.25 (quintet, J = 6 Hz, 2H), 1.45 (hextet, J = 8 Hz, 2H), 1.11 (t, J = 7 Hz, 3H), 0.81 (t, J = 7 Hz, 3H); TOF MS ES^{+} exact mass calculated for $C_{29}H_{32}N_3O_6$ (p+1): m/z = 518.2291. Found: 518.2302. IR ($CHCl_3$, cm^{-1}) 2965, 1738, 1454.

Anal. Calcd for $C_{29}H_{31}N_3O_6$: C, 67.30; H, 6.04; N, 8.12. Found: C, 67.15; H, 5.98; N, 7.93.

Example 7

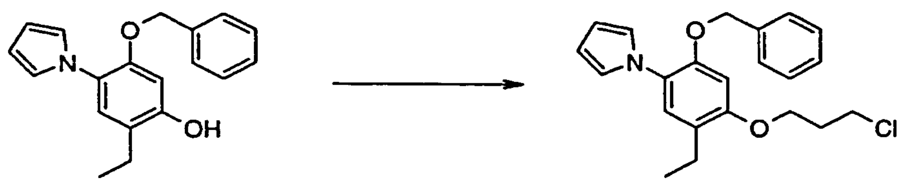
Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-pyrrol-1-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester.



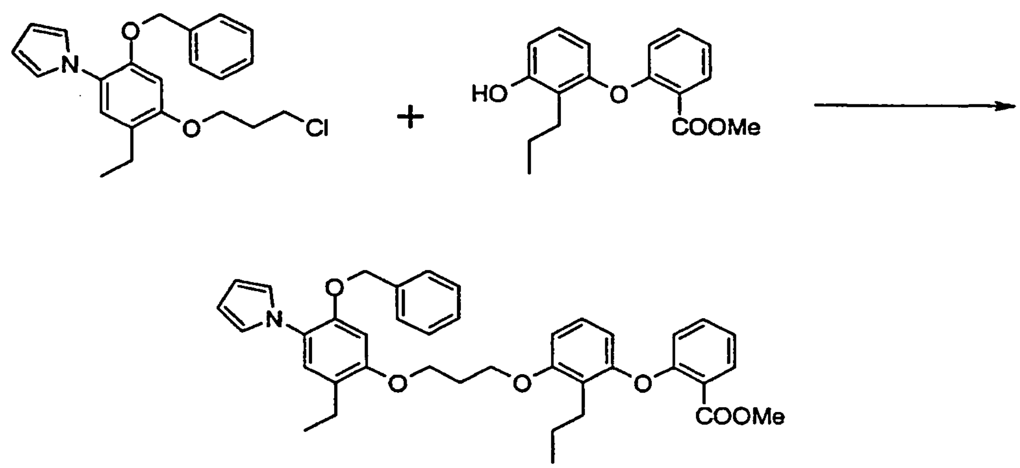
A. Preparation of 5-benzyloxy-2-ethyl-4-pyrrol-1-yl-phenol.

To a mixture of potassium nitrosodisulfonate (40.0 g, 149 mmol) and potassium hydrogen phosphate (10 g) in water (1.2 L) at room temperature was added a solution of 4-ethylbenzene-1,3-diol (10.0 g, 2.37 mmol) and potassium hydrogen phosphate (10.5 g) in water (150 mL). The mixture was stirred for 15 min and adjusted to pH ~3. The solution was extracted three times with diethyl ether. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in acetonitrile (70 mL) and treated at room temperature with 65% 3-pyrroline (12 mL). The resulting mixture was stirred for 1 h and concentrated in vacuo, dissolved in ethyl acetate and hexane, and filtered down a short column of silica gel. The resulting solution was concentrated in vacuo. The residue was dissolved in N,N-dimethylformamide (10 mL) and treated with benzyl bromide (0.85 mL, 7.1 mmol) and potassium carbonate (960 mg, 6.9 mmol) at room temperature for 15 h. The mixture was diluted with ethyl acetate, washed four times with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, ethyl acetate/hexane gradient) of the residue provided 316 mg (2%) of the title compound. TOF MS ES^+ exact mass calculated for $C_{19}H_{20}NO_2$ (p+1): m/z = 294.1494. Found: 294.1471.

B. Preparation of 1-[2-benzyloxy-4-(3-chloropropoxy)-5-ethylphenyl]-1*H*-pyrrole.



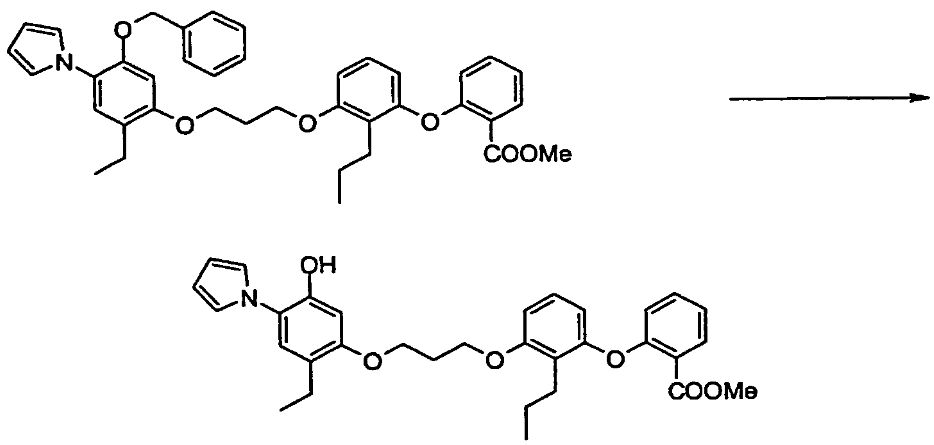
A mixture of 5-benzyloxy-2-ethyl-4-pyrrol-1-yl-phenol (316 mg, 1.08 mmol), potassium carbonate (223 mg, 1.62 mmol), and 1-bromo-3-chloropropane (0.16 mL, 1.6 mmol) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 18 h. The mixture was diluted with ethyl acetate and water, washed four times with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 5% ethyl acetate/95% hexane) of the residue provided 314 mg (79%) of the title compound as a colorless oil. TOF MS ES^+ exact mass calculated for $C_{22}H_{25}NClO_2$ (p+1): m/z = 370.1574. Found: 370.1548.



C. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-pyrrol-1-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A mixture of 1-[2-benzyloxy-4-(3-chloropropoxy)-5-ethylphenyl]-1*H*-pyrrole (310 mg, 0.85 mmol) and sodium iodide (140 mg, 0.94 mol) in 2-butanone (5 mL) was heated at reflux for 6 h. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. The residue was dissolved in N,N-dimethylformamide (7 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (242 mg, 0.85 mmol) and potassium carbonate (129 g, 93 mmol) at room temperature for 15 h. The mixture was diluted with ethyl acetate and water, washed four times with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 5% ethyl acetate/95% hexane) of the residue provided 196 mg (37%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 8, 2 Hz, 1H), 7.37 (dt, J = 8, 2 Hz, 1H), 7.30 (m, 5H), 7.07 (m, 3H), 6.84

(m, 2H), 6.79 (d, J = 8 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.58 (s, 1H), 6.42 (d, J = 8 Hz, 1H), 6.29 (m, 2H), 4.92 (s, 2H), 4.17 (t, J = 6 Hz, 2H), 4.15 (t, J = 6 Hz, 2H), 3.83 (s, 3H), 2.65 (t, J = 8 Hz, 2H), 2.58 (q, J = 7 Hz, 2H), 2.30 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 8 Hz, 2H), 1.16 (t, J = 7 Hz, 3H), 0.80 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{39}H_{42}NO_6$ (p+1): m/z = 620.3012. Found: 620.3021.

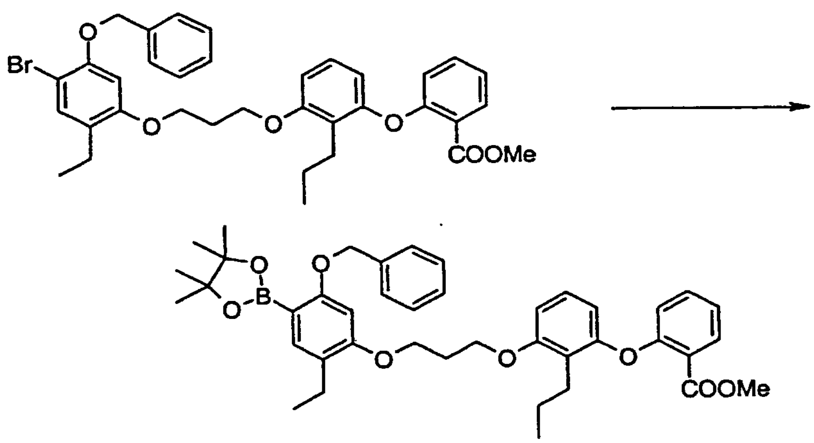


D. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-pyrrol-1-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester. A solution of 2-{3-[3-(5-benzyloxy-2-ethyl-4-pyrrol-1-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (195 mg, 0.315 mmol) in ethanethiol (5 mL) was treated with boron trifluoride etherate (1.3 mL, 9.5 mmol) at room temperature for 2.5 h. The mixture was diluted with diethyl ether and water. The organic layer was washed with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered, and concentrated in vacuo.

Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 39 mg (23%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.89 (d, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.07 (m, 2H), 6.98 (s, 1H), 6.68 (m, 3H), 6.65 (d, J = 8 Hz, 1H), 6.57 (s, 1H), 6.42 (d, J = 8 Hz, 1H), 6.35 (m, 2H), 5.04 (bs, 1H), 4.19 (m, 2H), 3.83 (s, 3H), 2.64 (t, J = 8 Hz, 2H), 2.58 (q, J = 7 Hz, 2H), 2.32 (quintet, J = 6 Hz, 2H), 1.55 (m, 2H), 1.14 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); TOF MS ES^+ exact mass calculated for $C_{32}H_{36}NO_6$ (p+1): m/z = 530.2543. Found: 530.2516.

Example 8

Preparation of 2-(3-{3-[4-(3-Bromo-[1,2,4]thiadiazol-5-yl)-2-ethyl-5-hydroxyphenoxy]-propoxy}-2-propylphenoxy)benzoic acid.

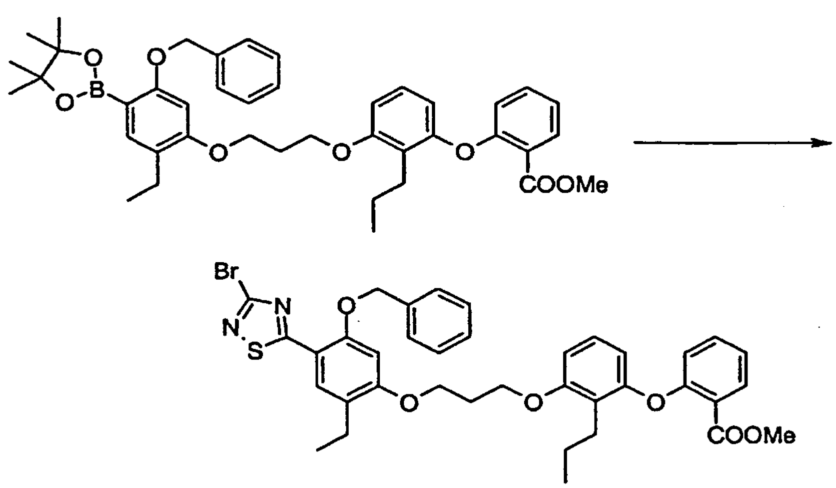


A. Preparation of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A mixture of 2-{3-[3-(5-benzyloxy-4-bromo-2-ethylphenoxy)propoxy]-2-propylphenoxy}-benzoic acid methyl ester (8.30 g, 13.1 mmol), triethylamine (5.2 mL, 39 mmol), and $PdCl_2$(dppf) (320 mg, 0.39 mmol) in de-oxygenated toluene (80 mL) was treated with a 1 M solution of 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane in tetrahydrofuran (20 mL, 20 mmol) and heated at reflux for 6 h. The mixture was filtered down a short column of silica gel and the filtrate concentrated in vacuo. Chromatography (silica gel, 35% ethyl acetate/65% hexane) of the residue provided a dark oil

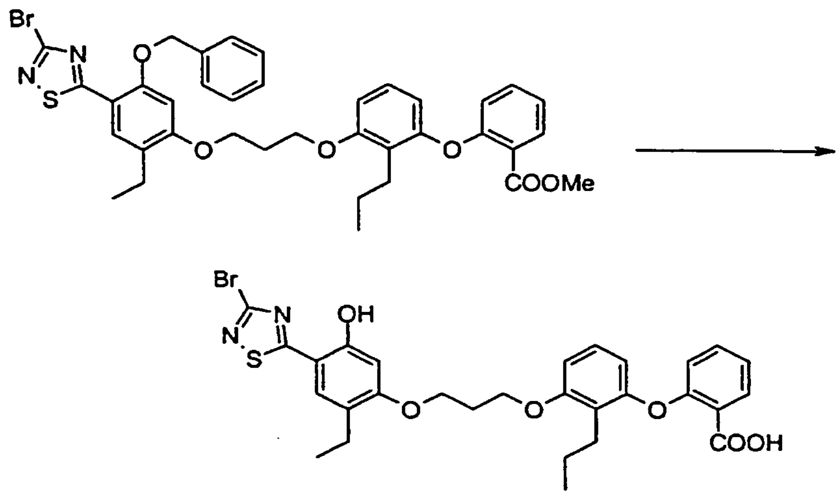
that was subjected to further chromatography (silica gel, hexane to 30% ethyl acetate/70% hexane) to give 7.70 g (84%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 8, 2 Hz, 1H), 7.60 (d, J = 8 Hz, 2H), 7.47 (s, 1H), 7.34 (m, 3H), 7.24 (t, J = 8 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 7.04 (d, J = 9 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 6.66 (d, J = 9 Hz, 1H), 6.47 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.07 (s, 2H), 4.18 (m, 4H), 3.81 (s, 3H), 2.64 (t, J = 8 Hz, 2H), 2.56 (q, J = 7 Hz, 2H), 2.30 (quintet, J = 6 Hz, 2H), 1.53 (hextet, J = 8 Hz, 2H), 1.34 (s, 12H),1.14 (t, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H); TOF MS ES$^+$ exact mass calculated for $C_{41}H_{53}NBO_8$ (p + NH_4): m/z = 698.3864. Found: 698.3889. IR ($CHCl_3$, cm^{-1}) 2964, 1720, 1604, 1453.

Anal. Calcd for $C_{41}H_{49}BO_8$: C, 72.35; H, 7.26. Found: C, 72.30; H, 7.12.



B. Preparation of 2-(3-{3-[5-benzyloxy-4-(3-bromo-[1,2,4]thiadiazol-5-yl)-2-ethyl-phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A mixture of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (310 mg, 0.46 mmol), 3-bromo-5-chloro-1,2,4-thiadiazole (120 mg, 0.60 mmol), cesium carbonate (300 mg, 0.92 mmol), and $PdCl_2$(dppf) (20 mg, 0.024 mmol) in de-oxygenated toluene (10 mL) was heated at 100 °C for 15 h. The mixture was diluted with a solution of 35% ethyl acetate/65% hexane and filtered down a short column of silica gel. The filtrate was concentrated in vacuo. Chromatography (silica gel, hexane to 30% ethyl acetate/70% hexane) of the residue provided 232 mg (70%) of the title compound. ^1H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.87 (dd, J = 8, 2 Hz, 1H), 7.44 (m, 2H), 7.37 (m, 4H), 7.08 (t, dJ = 8, 1 Hz, 1H), 7.04 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 6.66 (d, J = 9 Hz, 1H), 6.55 (s, 1H), 6.43 (d, J = 8 Hz, 1H), 5.28 (s, 2H), 4.21 (t, J = 6 Hz, 2H), 4.19 (t, J = 6 Hz, 2H), 3.81 (s, 3H), 2.62 (m, 4H), 2.34 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 8 Hz, 2H), 1.17 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 3H); MS ES^+ m/e 717, 719.



C. Preparation of 2-(3-{3-[4-(3-bromo-[1,2,4]thiadiazol-5-yl)-2-ethyl-5-hydroxyphenoxy]propoxy}-2-propylphenoxy)benzoic acid.

A solution of 2-(3-{3-[5-benzyloxy-4-(3-bromo-[1,2,4]thiadiazol-5-yl)-2-ethyl-phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (230 mg, 0.31 mmol) in ethanethiol (4 mL) was treated with boron trifluoride etherate (0.32 mL, 2.5 mmol) at room temperature for 6 h, at which time an additional portion of boron trifluoride etherate was added and stirring continued for 7 h. The reaction mixture was diluted with water, concentrated in vacuo, and extracted with diethyl ether. The residue was dissolved in methanol (5 mL) and treated with 1 N lithium hydroxide solution (2 mL) at 65 °C for 1 h. The mixture was concentrated in vacuo and the residue diluted with water and adjusted to ~pH 3 with 1 N hydrochloric acid. The resulting precipitate was collected via vacuum filtration and dissolved in dilute aqueous base. Reverse phase chromatography (1:1 acetonitrile/water) provided 43 mg (23%)

of the title compound as a yellow solid. ^1H NMR (DMSO-d_6) δ 7.85 (s, 1H), 7.80 (dd, J = 8, 2 Hz, 1H), 7.45 (m, 2H), 7.15 (m, 3H), 6.83 (d, J = 9 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 6.62 (s, 1H), 6.35 (d, J = 9 Hz, 1H), 4.20 (m, 4H), 2.55 (m, 4H), 2.27 (quintet, J = 5 Hz, 2H), 1.44 (hextet, J = 8 Hz, 2H), 1.13 (t, J = 7 Hz, 3H), 0.81 (t, J = 7 Hz, 3H); MS ES^+ m/e 551 ($p+NH_4^+-Br$); IR (KBr, cm^{-1}) 2900, 1696, 1603, 1461. Anal. Calcd for $C_{29}H_{29}BrN_2O_6S$: C, 56.77; H, 4.76; N, 4.56. Found: C, 56.63; H, 4.72; N, 3.98.

Example 9

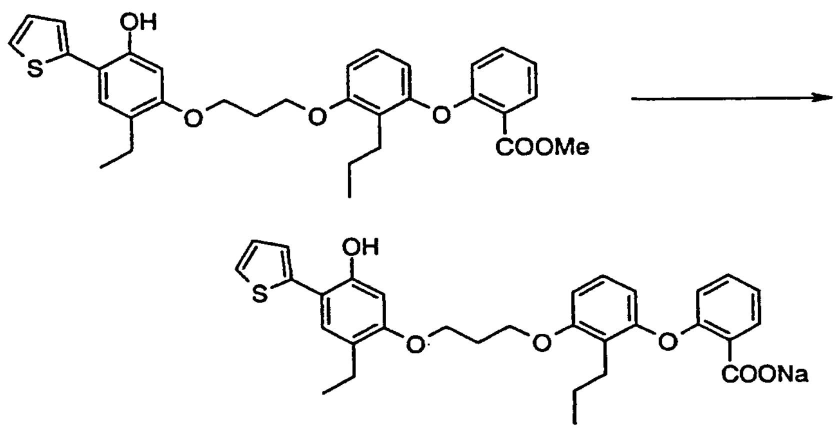
Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-thiophen-2-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid sodium salt.

A. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiophen-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A mixture of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (300 mg, 0.44 mmol), 2-bromothiophene (110 mg, 0.66 mmol), cesium carbonate (300 mg, 2.17 mmol), and $PdCl_2$(dppf) (20 mg, 0.024 mmol) in de-oxygenated toluene (10 mL) was heated at 105 °C for 66 h. The mixture was cooled to room temperature and concentrated

in vacuo. The residue was dissolved in methylene chloride and filtered down a short column of silica gel. The filtrate was concentrated in vacuo. Chromatography (silica gel, 30% ethyl acetate/70% hexane) of the residue provided an oil that was dissolved in ethanethiol (4 mL) and treated with boron trifluoride etherate (0.44 mL, 3.4 mmol) at room temperature for 3 h. The mixture was diluted with water and extracted with diethyl ether. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, hexane to 30% ethyl acetate/70% hexane) of the residue provided 120 mg (50%) of the title compound as a yellow film. ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, J = 8, 2 Hz, 1H), 7.35 (t, J = 8 Hz, 1H), 7.15 (d, J = 7 Hz, 1H), 7.03-7.15 (m, 5H), 6.80 (d, J = 9 Hz, 1H), 6.66 (d, J = 9 Hz, 1H), 6.51 (s, 1H), 6.42 (d, J = 8 Hz, 1H), 5.44 (bs, 1H), 4.18 (m, 4H), 3.82 (s, 3H), 2.62 (t, J = 8 Hz, 2H), 2.58 (q, J = 7 Hz, 2H), 2.54 (quintet, J = 6 Hz, 2H), 1.52 (hextet, J = 8 Hz, 2H), 1.16 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); MS ES^- m/e 545 (p - 1).

B. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiophen-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid sodium salt.

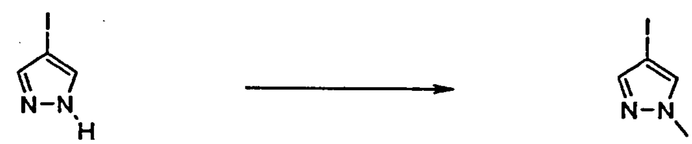


A solution of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiophen-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (120 mg, 0.22 mmol) in methanol (3 mL) was treated with 1 N lithium hydroxide solution (0.5 mL) at room temperature for 1 h and then with an additional portion of 1 N lithium hydroxide solution (0.75 mL) for 18 h. The mixture was heated at 50 °C then concentrated in vacuo. The residue was acidified with dilute hydrochloric acid and extracted with diethyl ether. The organic layer was washed once with water and concentrated in vacuo. The residue was diluted with 1 N sodium hydroxide solution (0.22 mL), diethyl ether, and toluene. The mixture was concentrated in vacuo, dissolved in methylene chloride, and concentrated in vacuo to provide 120 mg (98%) of the title compound as a green film. ^{1}H NMR (DMSO-d_6) δ 7.71 (d, J = 8 Hz, 1H), 7.42 (m, 2H), 7.31 (m, 2H), 7.10 (m, 2H), 6.99 (m, 1H), 6.76 (t, J = 7 Hz, 2H),

6.52 (s, 1H), 6.30 (d, J = 8 Hz, 1H), 4.16 (t, J = 7 Hz, 2H), 4.07 (t, J = 7 Hz, 2H), 2.50 (m, 4H), 2.20 (m, 2H), 1.40 (m, 2H), 1.06 (t, J = 8 Hz, 3H), 0.77 (t, J = 7 Hz, 3H); MS ES^+ m/e 533 (p + 1 - Na^+). IR ($CHCl_3$, cm^{-1}) 2900, 1738, 1604, 1454.

Example 10

Preparation of 2-(3-{3-[2-Ethyl-5-hydroxy-4-(1-methyl-1*H*-pyrazol-4-yl)-phenoxy]propoxy}-2-propylphenoxy)benzoic acid.



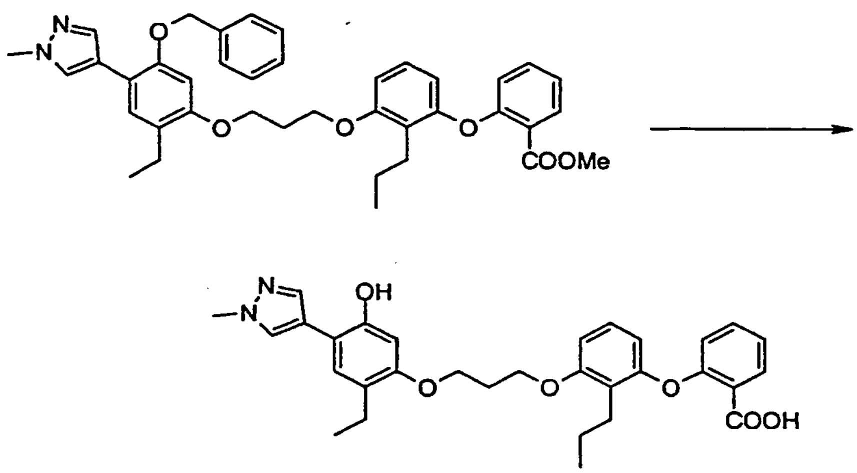
A. Preparation of 4-iodo-1-methylpyrazole (Known compound: RN 39806-90-1).

To a solution of 4-iodopyrazole (1.3 g, 6.8 mmol) in dioxane (10 mL) was added iodomethane (0.42 mL, 6.8 mmol) and the resulting mixture stirred at room temperature for 96 h. The mixture was concentrated in vacuo and the residue mixed with methylene chloride and filtered. The filtrate was concentrated in vacuo to provide 1.35 g (95%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.38 (s, 1H), 3.90 (s, 3H).

B. Preparation of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(1-methyl-1*H*-pyrazol-4-yl)phenoxy]-propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A mixture of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (1.00 g, 1.47 mmol),

4-iodo-1-methylpyrazole (450 mg, 2.16 mmol), cesium carbonate (1.20 g, 3.62 mmol), and $PdCl_2$(dppf) (72 mg, 0.088 mmol) in de-oxygenated toluene (35 mL) was heated at 100 °C for 24 h. Additional portions of 4-iodo-1-methylpyrazole (~30 mg) and $PdCl_2$(dppf) (~30 mg) were added and heating continued at 100 °C for 40 h. The mixture was cooled to room temperature, concentrated in vacuo, diluted with methylene chloride, and filtered down a short plug of silica gel. The filtrate was concentrated in vacuo. Chromatography (silica gel, 35% ethyl acetate/65% hexane to 65% ethyl acetate/35% hexane) of the residue provided 710 mg (76%) of the title compound. ^1H NMR ($CDCl_3$) δ 7.86 (dd, J = 8, 2 Hz, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.37 (m, 6H), 7.28 (s, 1H), 7.09 (d, J = 9 Hz, 1H), 7.04 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 6.67 (d, J = 9 Hz, 1H), 6.56 (s, 1H), 6.42 (d, J = 8 Hz, 1H), 5.08 (s, 2H), 4.18 (t, J = 6 Hz, 2H), 4.15 (t, J = 6 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 2.63 (t, J = 8 Hz, 2H), 2.59 (q, J = 7 Hz, 2H), 2.30 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 8 Hz, 2H), 1.23 (t, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H).



C. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(1-methyl-1*H*-pyrazol-4-yl)-phenoxy]propoxy}-2-propylphenoxy)benzoic acid.

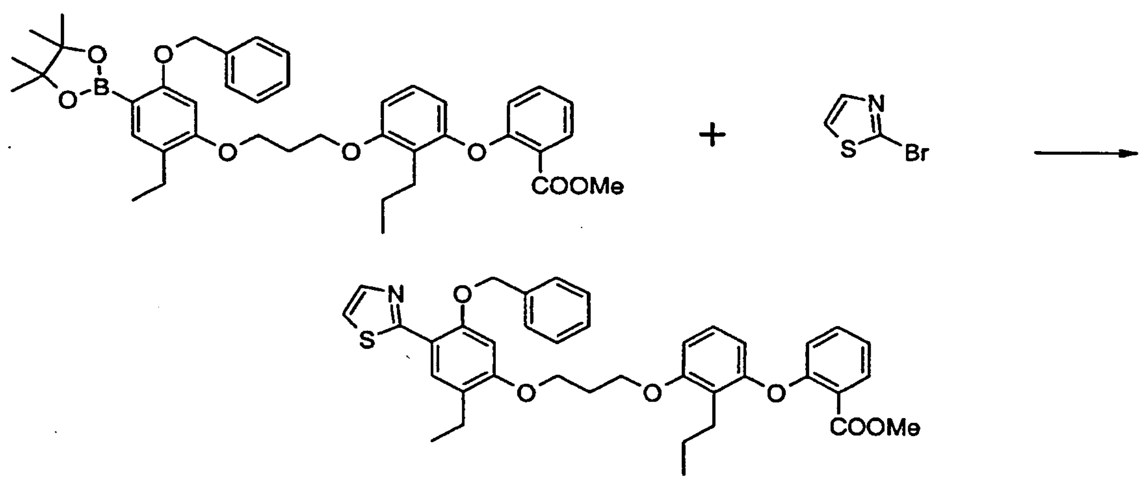
A solution of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(1-methyl-1*H*-pyrazol-4-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (710 mg, 1.12 mmol) in ethanethiol (5 mL) was treated with boron trifluoride etherate (1.42 mL, 11.2 mmol) at room temperature for 20 h. The reaction mixture was diluted with water, concentrated in vacuo, and extracted with diethyl ether. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. The residue was triturated twice with hexane and the residue dissolved in methanol (5 mL). This solution was treated with 1 N lithium hydroxide solution (5 mL) at ~95 °C for 2 h. The mixture was concentrated in vacuo and the residue diluted with water, washed twice with diethyl ether, and the aqueous layer acidified with 1 N hydrochloric acid. The resulting

solution was extracted with diethyl ether. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% methanol/90% methylene chloride) provided 338 mg (57%) of the title compound as a tan foam. ^{1}H NMR (DMSO-d_6) δ 12.85 (bs, 1H), 9.50 (bs, 1H), 7.98 (s, 1H), 7.78 (m, 2H), 7.48 (dt, J = 8, 2 Hz, 1H), 7.44 (s, 1H), 7.18 (t, J = 8 Hz, 1H), 7.13 (t, J = 9 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 6.77 (d, J = 9 Hz, 1H), 6.53 (s, 1H), 6.35 (d, J = 9 Hz, 1H), 4.20 (t, J = 6 Hz, 2H), 4.08 (t, J = 6 Hz, 2H), 3.85 (s, 3H), 2.50 (m, 4H), 2.24 (quintet, J = 5 Hz, 2H), 1.45 (hextet, J = 8 Hz, 2H), 1.09 (t, J = 7 Hz, 3H), 0.82 (t, J = 7 Hz, 3H); MS ES$^+$ m/e 531 (p+1); IR (KBr, cm^{-1}) 2961, 1697, 1602, 1460, 1222.

Anal. Calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 69.27; H, 6.08; N, 4.63.

Example 11

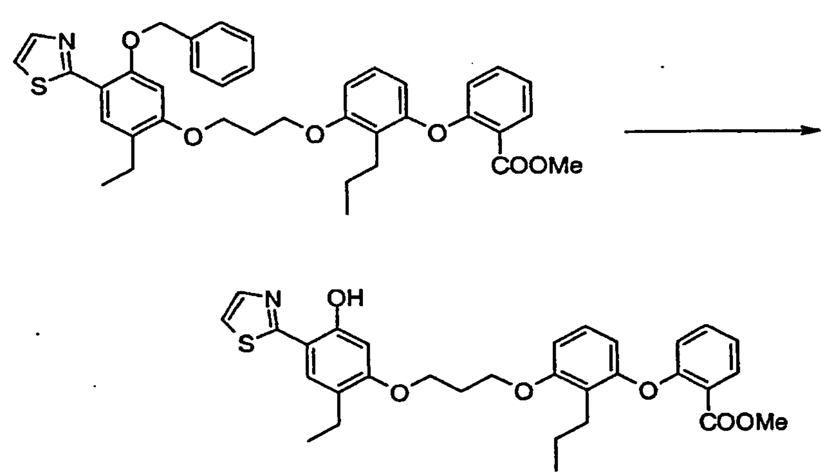
Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-thiazol-2-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid.



A. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-thiazol-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A mixture of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (960 mg, 1.41 mmol), 2-bromothiazole (0.25 mL, 2.8 mmol), cesium carbonate (1.15 g, 3.52 mmol), and $PdCl_2$(dppf) (35 mg, 0.040 mmol) in deoxygenated toluene (35 mL) was heated at 60 °C for 16 h then at 100 °C for 7 h. Additional portions of 2-bromothiazole (0.13 mL) and $PdCl_2$(dppf) (~30 mg) were added and heating continued at 100 °C for 72 h. The mixture was cooled to room temperature, concentrated in vacuo, diluted with

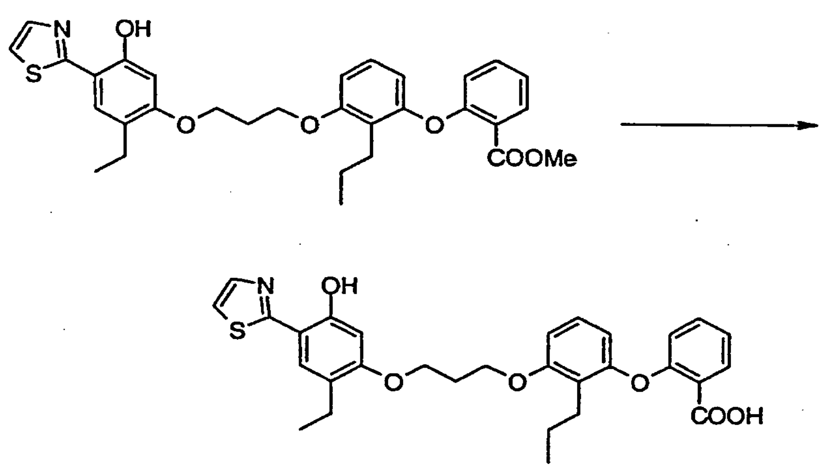
methylene chloride, and filtered down a short plug of silica gel. The filtrate was concentrated in vacuo. Chromatography (silica gel, hexane to 35% ethyl acetate/65% hexane) of the residue provided 282 mg (31%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 7.86 (dd, J = 8, 1 Hz, 1H), 7.82 (d, J = 3 Hz, 1H), 7.49 (d, J = 7 Hz, 2H), 7.35 (m, 4H), 7.23 (d, J = 3 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 7.04 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 6.65 (d, J = 9 Hz, 1H), 6.57 (s, 1H), 6.42 (d, J = 8 Hz, 1H), 5.24 (s, 2H), 4.17 (m, 4H), 3.81 (s, 3H), 2.63 (m, 4H), 2.33 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 8 Hz, 2H), 1.19 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 3H).



B. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiazol-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A solution of 2-{3-[3-(5-benzyloxy-2-ethyl-4-thiazol-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (282 mg, 0.442 mmol) in ethanethiol (3 mL) was treated with

boron trifluoride etherate (0.56 mL, 4.4 mmol) at room temperature for 3 h. The reaction mixture was diluted with water, concentrated in vacuo, and extracted with diethyl ether. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, ethyl acetate/hexane) provided 107 mg (44%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, J = 8, 2 Hz, 1H), 7.80 (d, J = 4 Hz, 1H), 7.35 (dt, J = 8, 2 Hz, 1H), 7.28 (d, J = 4 Hz, 1H), 7.24 (s, 1H), 7.09 (dt, J = 9, 2 Hz, 1H), 7.05 (t, J = 9 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 6.66 (d, J = 9 Hz, 1H), 6.61 (s, 1H), 6.42 (d, J = 9 Hz, 1H), 4.24 (t, J = 6 Hz, 2H), 4.18 (t, J = 6 Hz, 2H), 3.81 (s, 3H), 2.63 (t, J = 7 Hz, 2H), 2.58 (q, J = 7 Hz, 2H), 2.34 (quintet, J = 6 Hz, 2H), 1.52 (hextet, J = 8 Hz, 2H), 1.17 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 3H); MS ES^+ m/e 548 (p+1).

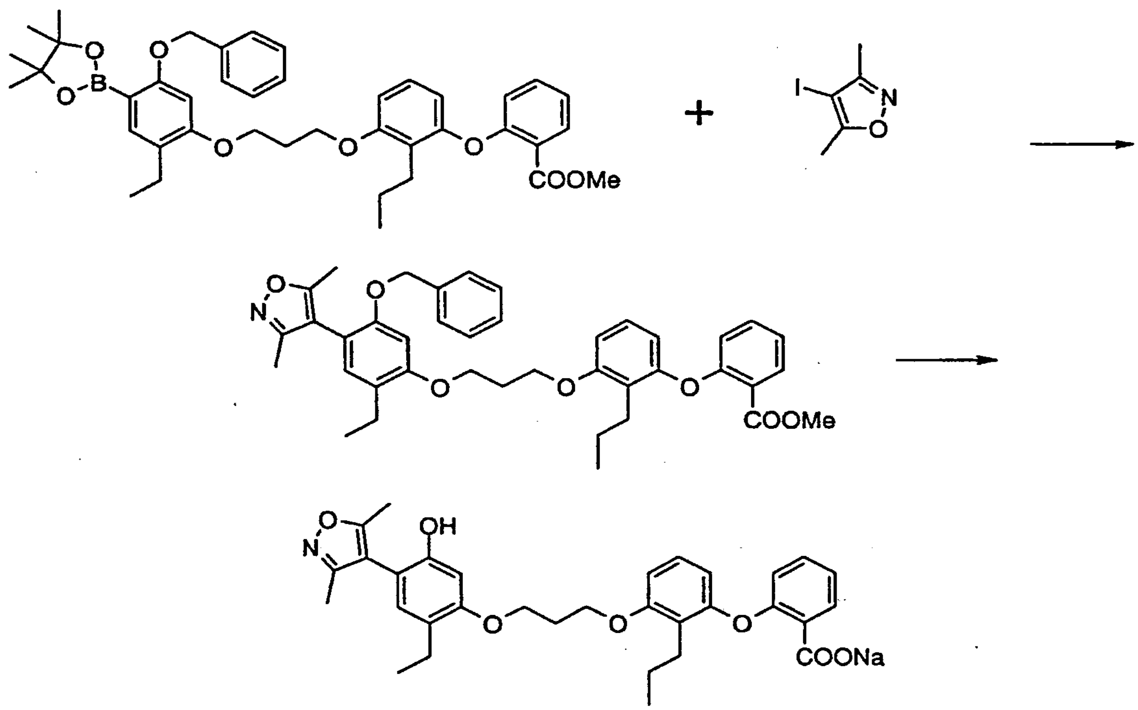


C. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-thiazol-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid.

2-{3-[3-(2-Ethyl-5-hydroxy-4-thiazol-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (107 mg, 0.196 mmol) was dissolved in a 1:1 solution of methanol/dioxane (3 mL) and treated with 1 N lithium hydroxide solution (1 mL) at 60 °C for 2 h. The mixture was concentrated in vacuo and the residue diluted with water, washed twice with diethyl ether, and the aqueous layer acidified with 1 N hydrochloric acid. The resulting solution was extracted twice with methylene chloride and the combined organic layers dried (magnesium sulfate), filtered, and concentrated in vacuo. Trituration (hexane) of the residue provided 72 mg (69%) of the title compound as a tan powder. ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, J = 8, 2 Hz, 1H), 7.70 (d, J = 4 Hz, 1H), 7.41 (dt, J = 8, 2 Hz, 1H), 7.35 (s, 1H), 7.18 (m, 3H), 6.82 (d, J = 9 Hz, 1H), 6.69 (d, J = 9 Hz, 1H), 6.62 (d, J = 9 Hz, 1H), 6.55 (s, 1H), 4.22 (t, J = 6 Hz, 2H), 4.21 (t, J = 6 Hz, 2H), 2.57 (m, 4H), 2.35 (quintet, J = 6 Hz, 2H), 1.49 (hextet, J = 8 Hz, 2H), 1.18 (t, J = 7 Hz, 3H), 0.86 (t, J = 7 Hz, 3H); MS ES$^+$ m/e 534 (p+1); IR (KBr, cm^{-1}) 2957, 1695, 1599, 1457. Anal. Calcd for $C_{30}H_{31}NO_6S$: C, 67.52; H, 5.86; N, 2.62. Found: C, 67.44; H, 5.95; N, 2.55.

Example 12

Preparation of 2-(3-{3-[4-(3,5-Dimethylisoxazol-4-yl)-2-ethyl-5-hydroxyphenoxy]propoxy}-2-propylphenoxy)benzoic acid sodium salt.

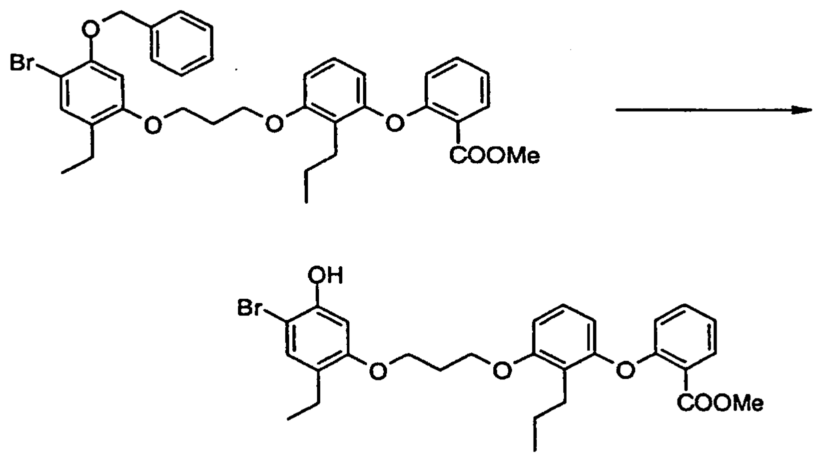


A mixture of 2-(3-{3-[5-benzyloxy-2-ethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (305 mg, 0.448 mmol), 3,5-dimethyl-4-iodoisoxazole (110 mg, 0.493 mmol), cesium carbonate (293 mg, 0.899 mmol), and $PdCl_2$(dppf) (15 mg, 0.018 mmol) in de-oxygenated toluene (10 mL) was heated at 95 °C for 10 h. Additional portions of 3,5-dimethyl-4-iodoisoxazole (110 mg), cesium carbonate (260 mg), and $PdCl_2$(dppf) (~15 mg) were added and heating continued at 110

°C for 20 h. The mixture was cooled to room temperature, concentrated in vacuo, diluted with methylene chloride, and filtered down a short plug of silica gel with 20% ethyl acetate/80% hexane. The filtrate was concentrated in vacuo. The resulting colorless oil was dissolved in methylene chloride (4 mL), cooled to 0 °C, and treated with iodotrimethylsilane (0.40 mL, 2.7 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 18 h. An additional portion of iodotrimethylsilane (0.70 mL) was added and stirring continued for 72 h. The mixture was poured into dilute sodium thiosulfate solution. The organic layer was separated, washed with water, dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting foam was dissolved in a 1:1 mixture of tetrahydrofuran/1 N hydrochloric acid (5 mL) and stirred at room temperature for 18 h. The mixture was concentrated in vacuo and treated with 1 equivalent 1 N sodium hydroxide solution in ether. The resulting mixture was concentrated in vacuo to provide 59 mg (23%) of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 7.40 (dd, J = 9, 2 Hz, 1H), 7.13 (dt, J = 8, 2 Hz, 1H), 6.97 (m, 2H), 6.79 (s, 1H), 6.68 (d, J = 9 Hz, 1H), 6.65 (d, J = 9 Hz, 1H), 6.60 (s, 1H), 6.21 (d, J = 8 Hz, 1H), 4.19 (t, J = 6 Hz, 2H), 4.01 (t, J = 6 Hz, 2H), 2.66 (t, J = 8 Hz, 2H), 2.48 (q, J = 8 Hz, 2H), 2.24 (s, 3H), 2.17 (quintet, J = 6 Hz, 2H), 2.07 (s, 3 H), 1.49 (hextet, J = 8 Hz, 2H), 1.07 (t, J = 7 Hz, 3H), 0.85 (t, J = 7 Hz, 3H); TOF MS ES$^+$ exact mass calculated for $C_{32}H_{36}NO_7$ (p+1): m/z = 546.2492. Found: 546.2514; IR (KBr, cm^{-1}) 3400, 1605, 1460.

Example 13

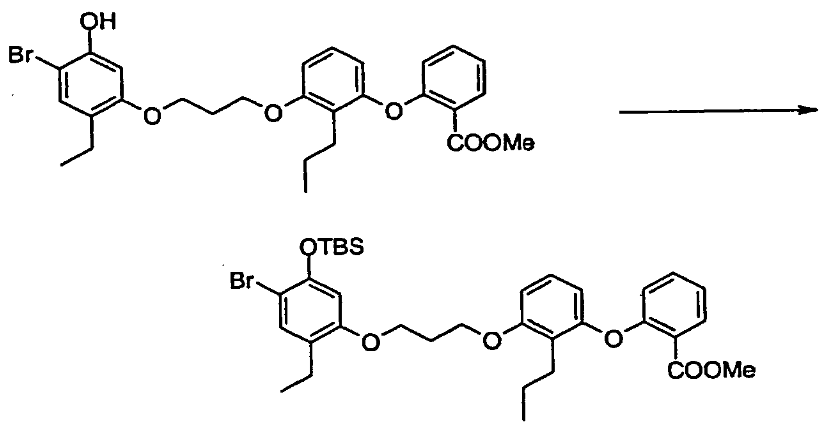
Preparation of 2-{3-[3-(2-Ethyl-4-furan-2-yl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}-benzoic acid sodium salt.



A. Preparation of 2-{3-[3-(4-bromo-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A solution of 2-{3-[3-(5-benzyloxy-4-bromo-2-ethylphenoxy)propoxy]-2-propylphenoxy}-benzoic acid methyl ester (2.50 g, 3.95 mmol) in methylene chloride (40 mL) was cooled to -70 °C and treated with boron tribromide (0.25 mL, 2.6 mmol). After 25 min the mixture was poured into cold water and the resulting mixture extracted with methylene chloride. The combined organic extracts were washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide 1.1 g (52%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 9 Hz, 1H), 7.38 (t, J = 8 Hz, 1H), 7.18 (s 1H), 7.12 (d, J = 9 Hz, 1H), 7.08

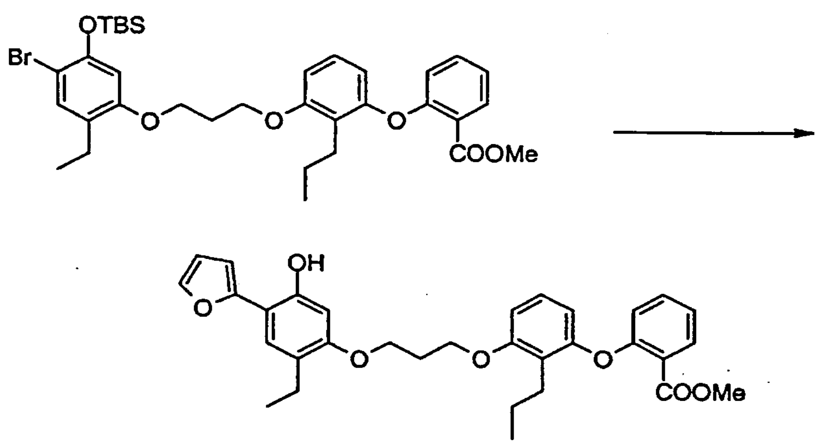
(d, J = 2 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 6.68 (d, J = 9 Hz, 1H), 6.56 (s, 1H), 6.46 (d, J = 9 Hz, 1H), 5.40 (s, 1H), 4.18 (t, J = 6 Hz, 2H), 4.11 (t, J = 6 Hz, 2H), 3.84 (s, 3H), 2.65 (t, J = 8 Hz, 2H), 2.54 (q, J = 7 Hz, 2H), 2.32 (quintet, J = 6 Hz, 2H), 1.54 (hextet, J = 8 Hz, 2H), 1.13 (t, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H); MS ES$^-$ m/z = 541 (M - H), 543 (M - H + 2).



B. Preparation of 2-(3-{3-[4-bromo-5-(*tert*-butyldimethylsilanyloxy)-2-ethylphenoxy]-propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A solution of 2-{3-[3-(4-bromo-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (1.00 g, 1.84 mmol) in methylene chloride (20 mL) was treated with imidazole (0.19 g, 2.8 mmol) and *tert*-butyldimethylsilyl chloride (0.388 g, 2.57 mmol) at room temperature for 2 h. The mixture was poured into water and the organic layer separated, washed once with water, once with saturated sodium chloride solution, filtered through a short pad of silica gel, and concentrated in vacuo to

provide 1.1 g (91%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 9 Hz, 1H), 7.38 (t, J = 8 Hz, 1H), 7.22 (s 1H), 7.12 (d, J = 9 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 6.69 (d, J = 9 Hz, 1H), 6.45 (d, J = 9 Hz, 1H), 6.40 (s, 1H), 4.20 (t, J = 6 Hz, 2H), 4.11 (t, J = 6 Hz, 2H), 3.83 (s, 3H), 2.64 (t, J = 8 Hz, 2H), 2.54 (q, J = 7 Hz, 2H), 2.32 (quintet, J = 6 Hz, 2H), 1.54 (hextet, J = 8 Hz, 2H), 1.13 (t, J = 7 Hz, 3H), 1.03 (s, 9H), 0.89 (t, J = 7 Hz, 3H), 0.23 (s, 6H).

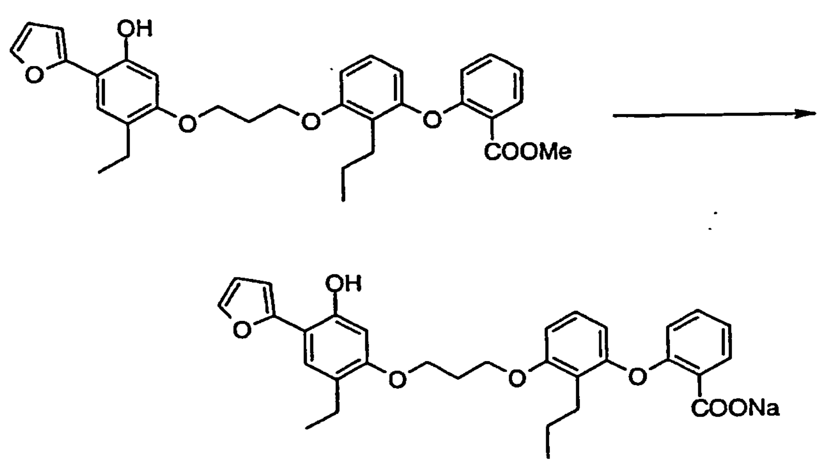


C. Preparation of 2-{3-[3-(2-ethyl-4-furan-2-yl-5-hydroxyphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester.

A mixture of 2-(3-{3-[4-bromo-5-(*tert*-butyldimethylsilanyloxy)-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (1.05 g, 1.60 mmol), furan-2-boronic acid (0.358 g, 3.20 mmol), tetrakis(triphenylphosphine)palladium(0) (0.185 g, 0.160 mmol), and 2 M aqueous sodium carbonate solution (8 mL) in

tetrahydrofuran (20 mL) was heated at reflux for 18 h. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was separated, washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 0.8 g (94%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 9 Hz, 1H), 7.48 (s, 1H), 7.38 (t, J = 8 Hz, 1H), 7.21 (s 1H), 7.13 (s, 1H), 7.10 (d, J = 9 Hz, 1H), 7.07 (d, J = 2 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 6.69 (d, J = 9 Hz, 1H), 6.52 (m, 3H), 6.44 (d, J = 9 Hz, 1H), 4.20 (m, 4H), 3.83 (s, 3H), 2.67 (t, J = 8 Hz, 2H), 2.59 (q, J = 7 Hz, 2H), 2.32 (quintet, J = 6 Hz, 2H), 1.55 (hextet, J = 8 Hz, 2H), 1.18 (t, J = 7 Hz, 3H), 0.91 (t, J = 7 Hz, 3H); MS ES^- m/z = 589 (p + AcO^-).

Anal. Calcd for $C_{32}H_{34}O_7$: C, 72.43; H, 6.46. Found: C, 72.21; H, 6.15.

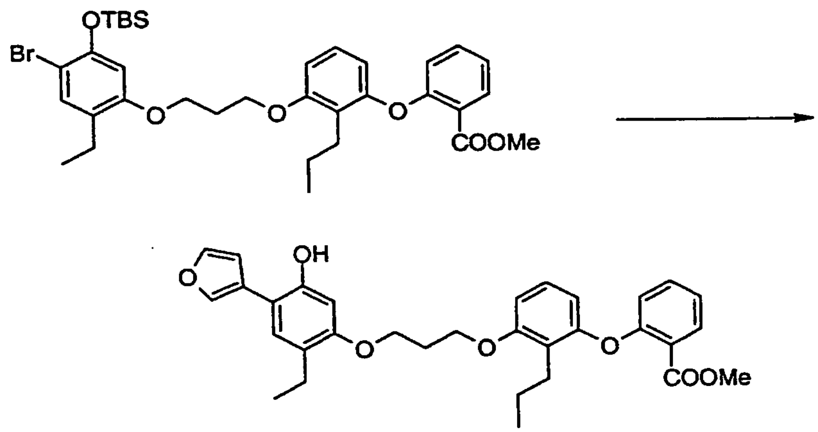


D. Preparation of 2-{3-[3-(2-ethyl-4-furan-2-yl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}benzoic acid sodium salt.

2-{3-[3-(2-Ethyl-4-furan-2-yl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (250 mg, 0.47 mmol) was dissolved in tetrahydrofuran (4 mL) and treated with 1 N lithium hydroxide solution (2 mL) at 50 °C for 16 h. The mixture was concentrated in vacuo and the residue diluted with water and extracted twice with ethyl acetate. The combined organic extracts were washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in ethyl acetate and shaken with 1 N hydrochloric acid. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in diethyl ether and treated with 1 N aqueous sodium hydroxide solution (0.32 mL). The mixture was concentrated in vacuo and azeotroped successively with diethyl ether, chloroform, and diethyl ether and dried to provide 168 mg (66%) of the title product as a cream solid. ^{1}H NMR (DMSO-d_6) δ 7.56 (s, 1H), 7.44 (d, J = 8 Hz, 1H), 7.35 (s, 1H), 7.13 (m, 1H), 6.97 (m, 2H), 6.77 (d, J = 2 Hz, 1H), 6.65 (m, 4H), 6.48 (d, J = 2 Hz, 1H), 6.24 (d, J = 9 Hz, 1H), 4.15 (t, J = 6 Hz, 2H), 3.96 (t, J = 6 Hz, 2H), 2.66 (t, J = 8 Hz, 2H), 2.42 (q, J = 7 Hz, 2H), 2.13 (quintet, J = 6 Hz, 2H), 1.48 (hextet, J = 8 Hz, 2H), 1.09 (t, J = 7 Hz, 3H), 0.84 (t, J = 7 Hz, 3H); TOF MS ES$^+$ exact mass calculated for $C_{31}H_{33}O_7$ (p+1): m/z = 517.2226. Found: 517.2230. IR (KBr, cm^{-1}) 3400, 2961, 1599, 1460.

Example 14

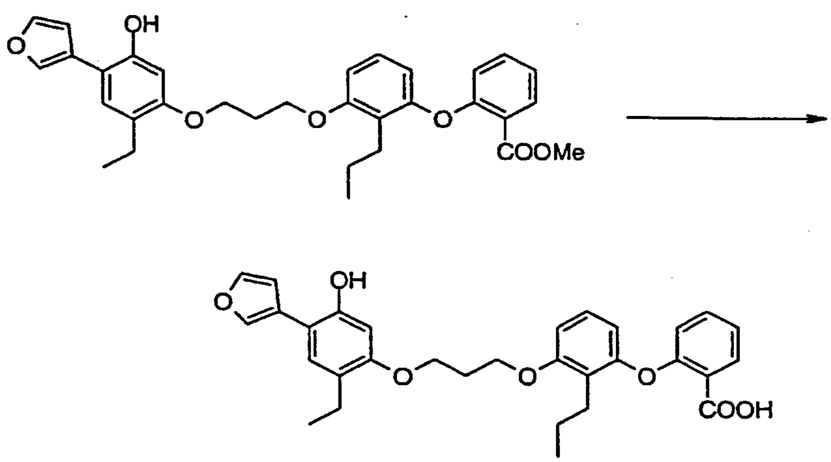
Preparation of 2-(3-{3-[2-Ethyl-5-hydroxy-4-furan-3-yl]phenoxy]propoxy}-2-propylphenoxy)benzoic acid.



A. Preparation of 2-{3-[3-(2-ethyl-4-furan-3-yl-5-hydroxyphenoxy)propoxy]-2-propyl-phenoxy}benzoic acid methyl ester.

A mixture of 2-(3-{3-[4-bromo-5-(*tert*-butyldimethylsilanyloxy)-2-ethylphenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (2.10 g, 3.19 mmol), furan-3-boronic acid (0.722 g, 6.45 mmol), tetrakis(triphenylphosphine)palladium(0) (0.37 g, 0.32 mmol), and 2 M aqueous sodium carbonate solution (16 mL) in tetrahydrofuran (30 mL) was heated at reflux for 48 h. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was separated, washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 15% ethyl acetate/85% hexane) of the residue provided 0.29 g

(17%) of the title compound as a yellow oil. TOF MS ES$^+$ exact mass calculated for $C_{32}H_{35}O_7$ (p+1): m/z = 531.2383. Found: 531.2396.



B. Preparation of 2-{3-[3-(2-ethyl-4-furan-3-yl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}benzoic acid sodium salt.

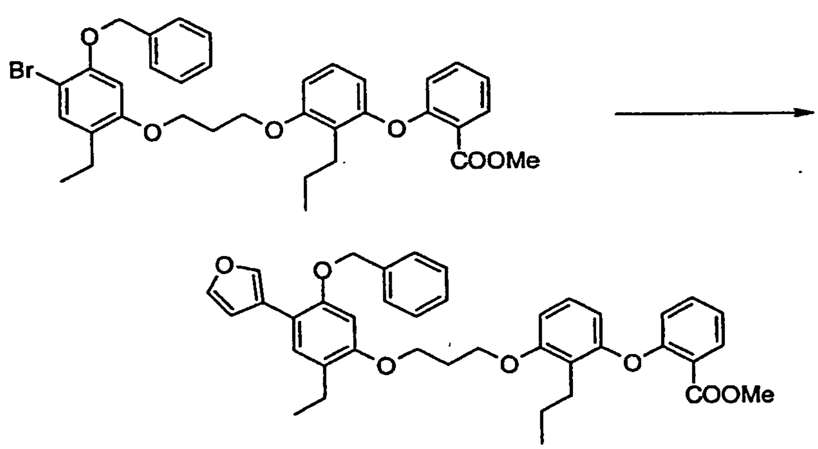
2-{3-[3-(2-Ethyl-4-furan-3-yl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (170 mg, 0.32 mmol) was dissolved in tetrahydrofuran (4 mL) and methanol (1 mL) and treated with 1 N lithium hydroxide solution (4 mL) at 50 °C for 2 h. The mixture was concentrated in vacuo and the residue acidified with hydrochloric acid and the resulting mixture extracted twice with ethyl acetate. The combined organic extracts were washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 2% methanol/98% chloroform) of the residue gave 45 mg of material that was again submitted to chromatography

(silica gel, 1% methanol/99% chloroform) to provide 25 mg (15%) of the title compound as an oil.

TOF MS ES$^+$ exact mass calculated for $C_{31}H_{33}O_7$ (p+1): m/z = 517.226. Found: 517.2230.

Example 15

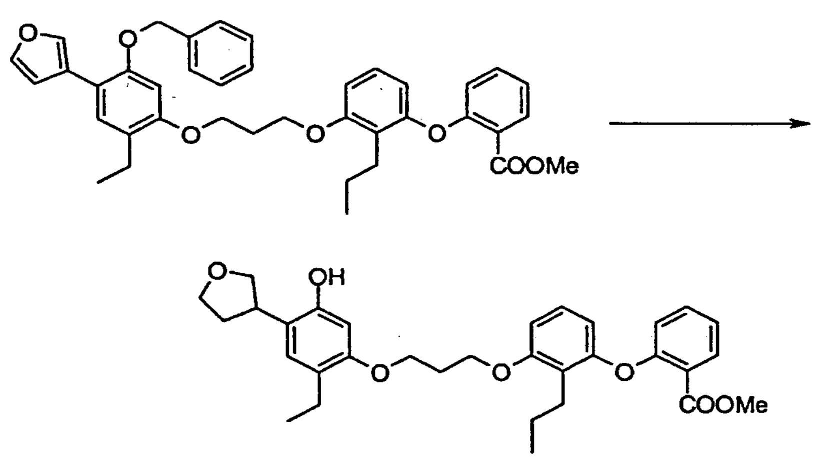
Preparation of 2-(3-{3-[2-Ethyl-5-hydroxy-4-(tetrahydrofuran-3-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid sodium salt hemihydrate.



A. Preparation of 2-{3-[3-(5-benzyloxy-2-ethyl-4-furan-3-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester.

A mixture of 2-{3-[3-(5-benzyloxy-4-bromo-2-ethylphenoxy)propoxy]-2-propylphenoxy}-benzoic acid methyl ester (3.00 g, 4.73 mmol), furan-3-boronic acid (1.06 g, 9.47 mmol), tetrakis(triphenylphosphine)palladium(0) (0.54 g, 0.47 mmol), and 2 M aqueous sodium carbonate solution (20 mL) in tetrahydrofuran (40 mL) was heated at 100 °C for 48

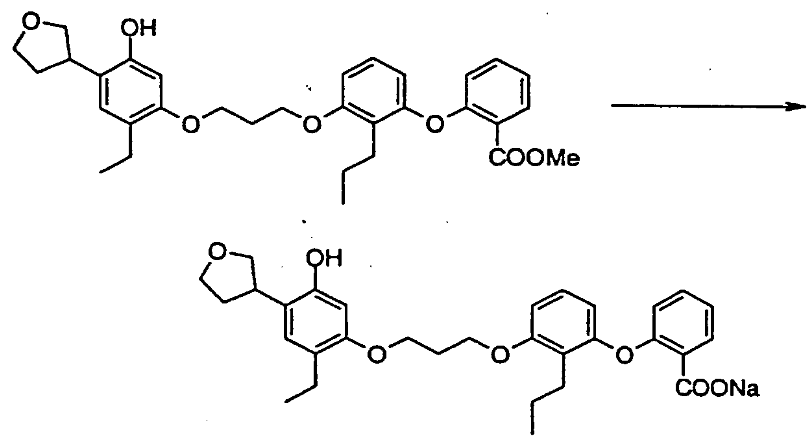
h. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was separated, washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 1.9 g (65%) of the title compound as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.88 (dd, J = 8, 2 Hz, 1H), 7.87 (s, 1H), 7.40 (m, 7H), 7.26 (s 1H), 7.05 (m, 2H), 6.80 (d, J = 9 Hz, 1H), 6.76 (d, J = 2 Hz, 1H), 6.67 (d, J = 9 Hz, 1H), 6.60 (s, 1H), 6.43 (d, J = 9 Hz, 1H), 5.11 (s, 2H), 4.18 (m, 4H), 3.83 (s, 3H), 2.66 (t, J = 8 Hz, 2H), 2.62 (q, J = 7 Hz, 2H), 2.30 (quintet, J = 6 Hz, 2H), 1.57 (hextet, J = 8 Hz, 2H), 1.20 (t, J = 7 Hz, 3H), 0.92 (t, J = 7 Hz, 3H); MS ES^+ m/z = 621 (p + 1); IR ($CHCl_3$, cm^{-1}) 3000, 1727, 1603, 1461.



B. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(tetrahydrofuran-3-yl)phenoxy]-propoxy}-2-propylphenoxy)benzoic acid methyl ester.

A solution of 2-{3-[3-(5-benzyloxy-2-ethyl-4-furan-3-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (1.8 g, 2.9 mmol) in ethyl acetate (40 mL) was treated with 10% palladium-on-carbon (0.39 g) and hydrogenated at 48 psi and 45 °C for 72 h. The mixture was cooled to room temperature, filtered through Celite™, and the filtrate concentrated in vacuo to provide 1.2 g (77%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, J = 8, 2 Hz, 1H), 7.57 (dt, J = 8, 2 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 7.04 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 6.80 (s, 1H), 6.67 (d, J = 9 Hz, 1H), 6.44 (d, J = 9 Hz, 1H), 6.43 (s, 1H), 4.19 (m, 3H), 4.10 (m, 2H), 4.02 (dd, J = 12, 3 Hz, 1H), 3.88 (dd, J = 12, 8 Hz, 1H), 3.84 (s, 3H), 3.73 (q, J = 9 Hz, 1H), 3.45 (m, 1H), 2.64 (t, J = 8 Hz, 2H), 2.53 (q, J = 7 Hz, 2H), 2.38 (m, 1H), 2.28 (quintet, J = 6 Hz, 2H), 1.99 (m, 1H), 1.55 (hextet, J = 8 Hz, 2H), 1.15 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H); MS ES^- m/z = 593 (p + CH_3COO^-); IR ($CHCl_3$, cm^{-1}) 2963, 1719, 1589, 1461.

Anal. Calcd for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 71.41; H, 7.06.



C. Preparation of 2-(3-{3-[2-ethyl-5-hydroxy-4-(tetrahydrofuran-3-yl)phenoxy]-propoxy}-2-propylphenoxy)benzoic acid sodium salt hemihydrate.

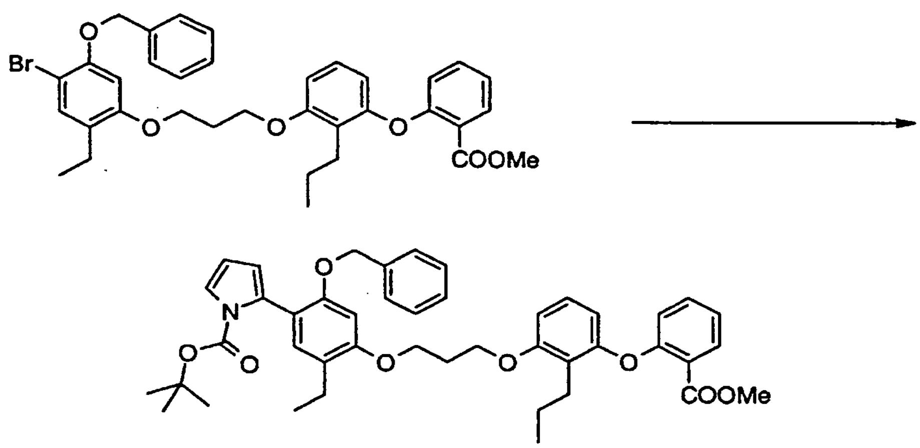
A solution of 2-(3-{3-[2-ethyl-5-hydroxy-4-(tetrahydrofuran-3-yl)phenoxy]propoxy}-2-propylphenoxy)benzoic acid methyl ester (0.92 g, 1.7 mmol) in tetrahydrofuran (10 mL) and methanol (5 mL) was treated with 1 M aqueous lithium hydroxide solution (10 mL) at 55 °C for 2 h. The mixture was allowed to cool to room temperature and stirred for an additional 18 h. The mixture was concentrated in vacuo and the remaining aqueous mixture was washed once with diethyl ether. The aqueous layer was acidified with concentrated hydrochloric acid and the resulting solution extracted with ethyl acetate. The ethyl acetate layer was washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting colorless oil was dissolved in diethyl ether and treated with 1 N aqueous sodium hydroxide solution (1.72 mL). The resulting biphasic mixture was diluted with chloroform and concentrated in vacuo. Diethyl ether was added and the mixture concentrated in vacuo. The resulting

white foam was dried in vacuo at room temperature for 60 h to provide 0.78 g (84%) of the title compound: mp 67-71 °C. ^{1}H NMR (DMSO-d_6) δ 7.62 (dd, J = 8, 2 Hz, 1H), 7.30 (dt, J = 8, 2 Hz, 1H), 7.05 (m, 2H), 6.85 (s, 1H), 6.73 (d, J = 9 Hz, 1H), 6.70 (d, J = 9 Hz, 1H), 6.53 (s, 1H), 6.34 (d, J = 9 Hz, 1H), 4.15 (t, J = 6 Hz, 2H), 4.04 (t, J = 6 Hz, 2H), 3.95 (m, 1H), 3.88 (m, 1H), 3.75 (q, J = 9 Hz, 1H), 3.49 (m 2H), 2.60 (t, J = 8 Hz, 2H), 2.45 (q, J = 7 Hz, 2H), 2.15 (m, 3H), 1.90 (m, 1H), 1.48 (hextet, J = 8 Hz, 2H), 1.06 (t, J = 7 Hz, 3H), 0.83 (t, J = 7 Hz, 3H); MS ES$^-$ m/z = 519 (p - Na^+); IR ($CHCl_3$, cm^{-1}) 2964, 1783, 1604, 1461.

Anal. Calcd for $C_{31}H_{35}NaO_7$ • 0.5 H_2O: C, 67.50; H, 6.58. Found: C, 67.76; H, 6.68.

Example 16

Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-pyrrolidin-2-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid hydrochloride hydrate.

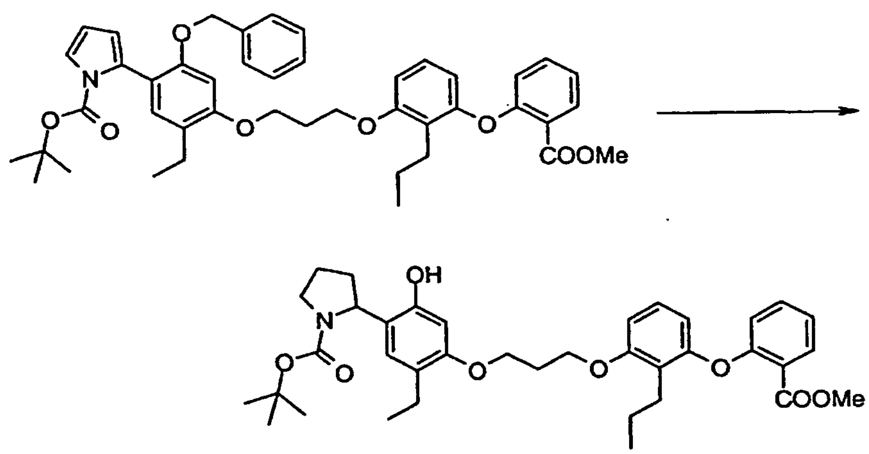


A. Preparation of 2-(2-benzyloxy-5-ethyl-4-{3-[3-(2-methoxycarbonylphenoxy)-2-propylphenoxy]propoxy}phenyl)pyrrole-1-carboxylic acid *tert*-butyl ester.

A mixture of 2-{3-[3-(5-benzyloxy-4-bromo-2-ethylphenoxy)propoxy]-2-propylphenoxy}benzoic acid methyl ester (3.00 g, 4.73 mmol), N-Boc pyrrole-2-boronic acid (1.99 g, 9.43 mmol), tetrakis(triphenylphosphine)palladium(0) (0.54 g, 0.47 mmol), and 2 M aqueous sodium carbonate solution (25 mL) in tetrahydrofuran (60 mL) was heated at reflux for 40 h. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was separated, washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered,

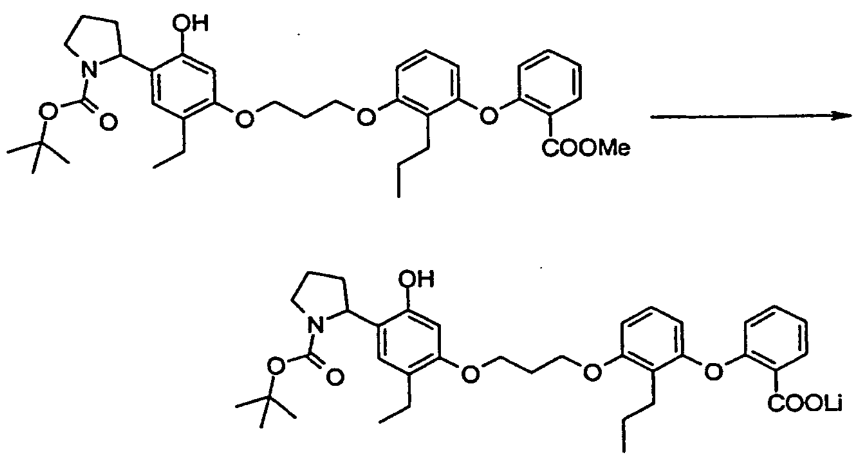
and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexane) of the residue provided 2.6 g (76%) of the title compound as a solid. ^1H NMR ($CDCl_3$) δ 7.88 (dd, J = 8, 2 Hz, 1H), 7.15-7.40 (m, 7H), 7.08 (m, 3H), 6.82 (d, J = 9 Hz, 1H), 6.68 (d, J = 9 Hz, 1H), 6.52 (s, 1H), 6.44 (d, J = 9 Hz, 1H), 6.23 (t, J = 4 Hz, 1H), 6.12 (m, 1H), 4.95 (s, 2H), 4.20 (t, J = 6 Hz, 2H); 4.15 (t, J = 6 Hz, 2H), 3.84 (s, 3H), 2.66 (t, J = 8 Hz, 2H), 2.60 (q, J = 7 Hz, 2H), 2.30 (quintet, J = 6 Hz, 2H), 1.57 (hextet, J = 8 Hz, 2H), 1.28 (s, 9H), 1.18 (t, J = 7 Hz, 3H), 0.93 (t, J = 7 Hz, 3H); TOS MS ES^+ exact mass calculated for $C_{44}H_{53}N_2O_8$ (p + NH_4^+): m/z = 737.3802. Found: 737.3804; IR ($CHCl_3$, cm^{-1}) 2964, 1730, 1461.

Anal. Calcd for $C_{44}H_{49}NO_8$: C, 73.41; H, 6.86; N, 1.94. Found: C, 73.76; H, 6.76; N, 2.04.



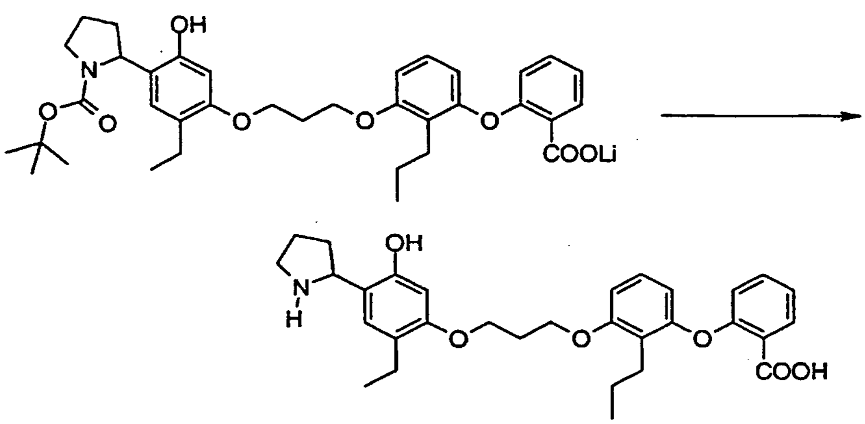
B. Preparation of 2-(5-ethyl-2-hydroxy-4-{3-[3-(2-methoxycarbonylphenoxy)-2-propylphenoxy]propoxy}phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

A solution of 2-(2-benzyloxy-5-ethyl-4-{3-[3-(2-methoxycarbonylphenoxy)-2-propylphenoxy]propoxy}phenyl)pyrrole-1-carboxylic acid *tert*-butyl ester (0.98 g, 1.4 mmol) in ethyl acetate (40 mL) was treated with 10% palladium-on-carbon (0.98 g) and hydrogenated at 45 psi and 45 °C for 25 h, at room temperature for 20 h, then at 45 °C for 19 h. The mixture was cooled to room temperature, filtered through Celite™, and the filtrate concentrated in vacuo to provide 0.76 g (88%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.87 (dd, J = 8, 2 Hz, 1H), 7.37 (dt, J = 8, 2 Hz, 1H), 7.10 (d, J = 9 Hz, 1H), 7.04 (d, J = 9 Hz, 1H), 6.91 (s, 1H), 6.81 (d, J = 9 Hz, 1H), 6.67 (d, J = 9 Hz, 1H), 6.47 (s, 1H), 6.44 (d, J = 9 Hz, 1H), 5.09 (m, 1H), 4.18 (d, J = 6 Hz, 2H), 4.14 (t, J = 6 Hz, 2H), 3.84 (s, 3H), 3.45 (m, 2H), 2.64 (t, J = 8 Hz, 2H), 2.54 (m, 3H), 2.25 (m, 5H), 2.06 (m, 1H), 1.54 (hextet, J = 8 Hz, 2H), 1.43 (s, 9H), 1.15 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H).



C. **Preparation of 2-(4-{3-[3-(2-carboxyphenoxy)-2-propylphenoxy]propoxy}-5-ethyl-2-hydroxyphenyl)pyrrolidine-1-carboxylic acid tert-butyl ester lithium salt hydrate.** A solution of 2-(5-ethyl-2-hydroxy-4-{3-[3-(2-methoxycarbonylphenoxy)-2-propylphenoxy]propoxy}phenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.114 g, 0.18 mmol) in a 1:1 mixture of methanol/tetrahydrofuran (4 mL) was treated with solution of 1 M lithium hydroxide (4 mL) at room temperature for 18 h. The mixture was concentrated in vacuo and the residue dissolved in water. The resulting mixture was extracted with ethyl acetate. The organic extract was dried (sodium sulfate), filtered, and concentrated in vacuo. The residue was diluted with diethyl ether, concentrated in vacuo, and dried to provide 90 mg (78%) of the title compound. MS ES$^+$ m/z = 620 (p + 1 - Li$^+$); IR (KBr, cm^{-1}) 2964, 1672, 1603, 1416.

Anal. Calcd for $C_{36}H_{44}NO_8Li \cdot H_2O$: C, 67.17; H, 7.20; N, 2.18. Found: C, 66.72; H, 6.99; N, 2.27.



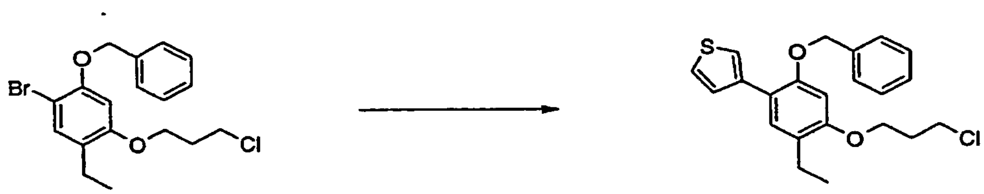
D. Preparation of 2-{3-[3-(2-ethyl-5-hydroxy-4-pyrrolidin-2-yl-phenoxy)propoxy]-2-propylphenoxy}benzoic acid hydrochloride hydrate.

Into a solution of 2-(4-{3-[3-(2-carboxyphenoxy)-2-propylphenoxy]propoxy}-5-ethyl-2-hydroxyphenyl)pyrrolidine-1-carboxylic acid tert-butyl ester lithium salt hydrate (0.100 g, 0.16 mmol) in anhydrous diethyl ether (5 mL) was bubbled gaseous HCl. The resulting mixture was allowed to stir for 1 h. The mixture was concentrated in vacuo. Chromatography (SCX cation exchange resin, 1:1 tetrahydrofuran/methanol to dilute ammonia/methanol) of the residue provided a tan solid. This material was dissolved in ether and treated with gaseous HCl. This mixture was concentrated in vacuo to provide 48 mg (52%) of the title compound. ^{1}H NMR (DMSO-d_6) δ 12.80 (bs, 1H), 10.12 (s, 1H), 9.34 (bs, 1H), 8.36 (bs, 1H), 7.79 (dd, J = 9, 2 Hz, 1H), 7.47 (dt, J = 8, 2 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 7.12 (d, J = 9 Hz, 1H), 7.07 (s, 1H), 6.80 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 6.58 (s, 1H), 6.35 (d, J = 9 Hz, 1H),

4.56 (m, 1H), 4.20 (t, J = 6 Hz, 2H); 4.11 (t, J = 6 Hz, 2H), 3.25 (m, 2H), 2.50 (m, 5H), 1.90-2.60 (m, 5H), 1.44 (hextet, J = 8 Hz, 2H), 1.08 (t, J = 7 Hz, 3H), 0.82 (t, J = 7 Hz, 3H); TOS MS ES^+ exact mass calculated for $C_{31}H_{38}NO_6$ (p + 1): m/z = 520.2699. Found: 520.2672.

Example 17

Preparation of 2-{3-[3-(2-Ethyl-5-hydroxy-4-thiophen-3-yl-phenoxy)propoxy]-2-propyl-phenoxy}benzoic acid hydrate.

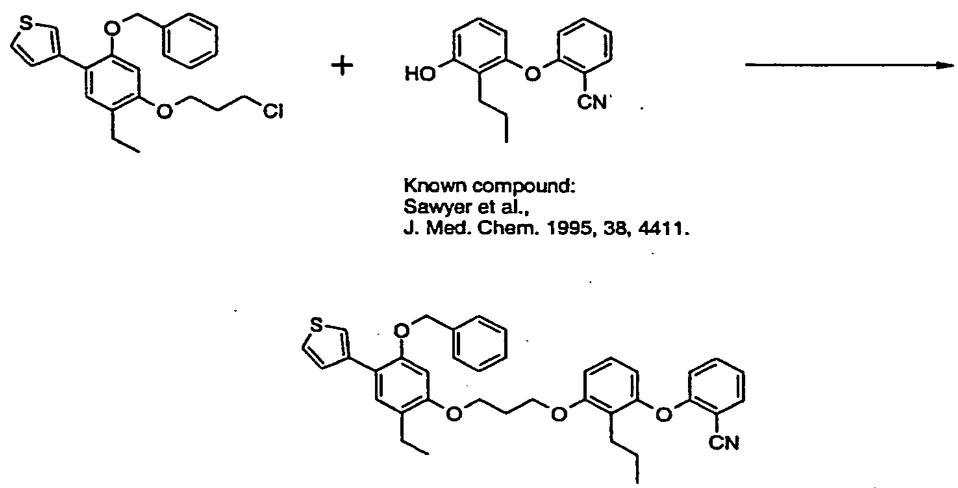


Known compound:
Sawyer et al., *J. Med. Chem.* **1995**, *38*, 4411.

A. Preparation of 3-[2-benzyloxy-4-(3-chloropropoxy)-5-ethylphenyl]thiophene. A mixture of 4-(benzyloxy)-5-bromo-2-(3-chloropropoxy)ethylbenzene (1.90 g, 5.30 mmol), 3-thiopheneboronic acid (2.00 g, 15.9 mmol), tetrakis(triphenylphosphine)palladium(0) (312 mg, 0.270 mmol), 2 M aqueous sodium carbonate solution (4 mL), and *n*-propanol (4 mL) in toluene (16 mL) was refluxed for 4 h. The mixture was cooled to room temperature, diluted with diethyl ether, washed once with water and once with saturated sodium chloride solution. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 5% ethyl acetate/95%

hexane) of the residue provided 1.54 g (80%) of the title product as a white solid: mp 65-67 °C. ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 2.8 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.45-7.30 (m, 7H), 6.62 (s, 1H), 5.13 (s, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.81 (t, J = 6.3 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 2.29 (quintet, J = 6.0 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H); MS FD m/e 386 (p); IR ($CHCl_3$, cm^{-1}) 2969, 1613, 1501, 1138.

Anal. Calcd for $C_{22}H_{23}O_2ClS$: C, 68.29; H, 5.99. Found: C, 68.53; H, 6.00.

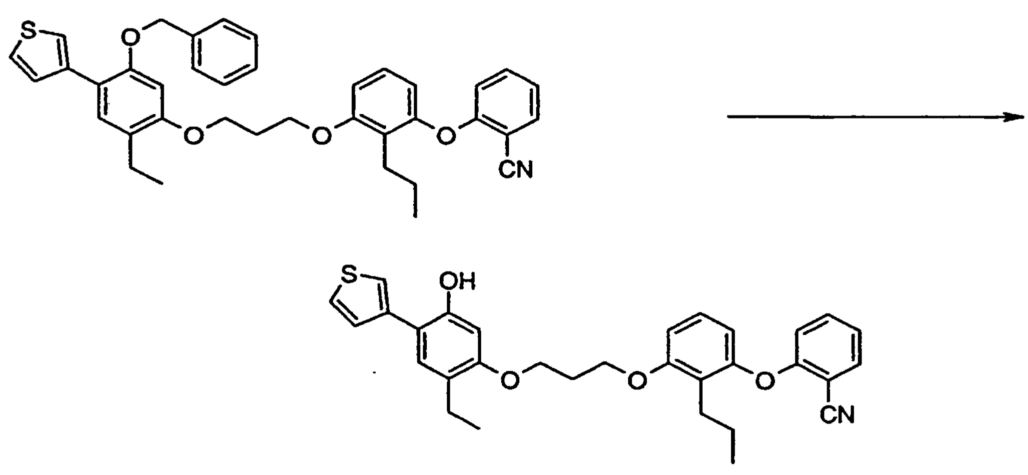


B. **Preparation of 2-[2-propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(thiophen-3-yl)phenoxy]propoxy]phenoxy]benzonitrile.**

A mixture of 4-(benzyloxy)-2-(3-chloropropoxy)-5-(thiophen-3-yl)ethylbenzene (1.25 g, 3.23 mmol), 3-(2-cyanophenoxy)-2-propylphenol (0.82 g, 3.2 mmol), potassium iodide (0.21 g, 1.3 mmol), potassium carbonate (1.12 g, 8.08 mmol), and methyl sulfoxide (2 mL) in 2-butanone (10 mL) was refluxed for 60 h. The mixture was cooled to room temperature,

diluted with ether, and washed with water. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 5% ethyl acetate/95% hexane) of the residue provided 1.31 g (67%) of the title product as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 2.9 Hz, 1H), 7.48 (d, J = 5.2 Hz, 1H), 7.45-7.25 (m, 8H), 7.20 (t, J = 8.2 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 6.64 (s, 1H), 6.63 (d, J = 6.4 Hz, 1H), 5.11 (s, 2H), 4.26 (t, J = 6.0 Hz, 2H), 4.22 (t, J = 6.0 Hz, 2H), 2.65 (m, 4H), 2.36 (quintet, J = 5.9 Hz, 2H), 1.58 (hextet, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS FD m/e 603 (p); IR ($CHCl_3$, cm^{-1}) 2967, 2250, 1613, 1501. Anal. Calcd for $C_{38}H_{37}NO_4S$: C, 75.59; H, 6.18; N, 2.32. Found: C, 74.65; H, 6.21; N, 2.57.

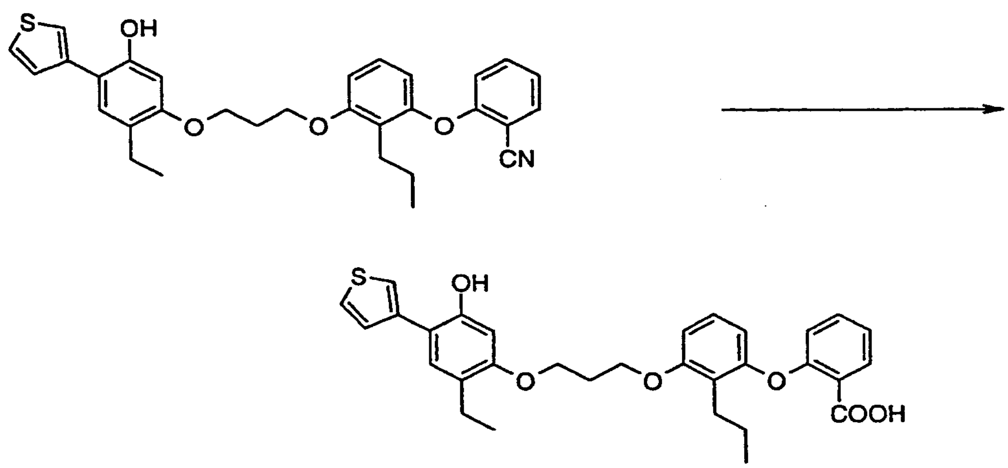
C. Preparation of 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(thiophen-3-yl)phenoxy]propoxy]phenoxy]benzonitrile.



To a solution of 2-[2-propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(thiophen-3-yl)phenoxy]propoxy]phenoxy]benzonitrile (900 mg,

1.49 mmol) in methylene chloride (25 mL) cooled to -78 °C was added 1 M boron tribromide solution in methylene chloride (2.99 mL, 2.99 mmol) over 2 min. The resulting deep violet solution was stirred for 30 min and allowed to warm to room temperature. The mixture was diluted with water and shaken. The organic layer was separated, dried (magnesium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 25% ethyl acetate, 75% hexane) provided 400 mg (52%) of the title product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 4.8 Hz, 1H), 7.71 (d, J = 4.9 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.62 (s, 1H), 7.42 (t, J = 7.1 Hz, 1H), 7.27 (t, J = 6.6 Hz, 1H), 7.20 (s, 1H), 7.08 (t, J = 6.9 Hz, 1H), 6.85 (s, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 4.71 (s, 1H, -OH), 4.26 (t, J = 6.0 Hz, 4H), 2.72 (q, J = 7.4 dHz, 2H), 2.59 (t, J = 7.3 Hz, 2H), 2.39 (quintet, J = 6.1 Hz, 2H), 1.54 (hextet, J = 7.7 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).

D. Preparation of 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(thiophen-3-yl)phenoxy]propoxy]phenoxy]benzoic acid hydrate.



A solution of 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(thiophen-3-yl)phenoxy]propoxy]phenoxy]benzonitrile (400 mg, 0.780 mmol) in 2:1 methanol/water (6 mL) was treated with 12.5 M aqueous sodium hydroxide (4.0 mL) at reflux for 36 h. The mixture was cooled to room temperature, diluted with water, and extracted once with diethyl ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted twice with methylene chloride. The combined methylene chloride layers were dried (magnesium sulfate), filtered, and concentrated in vacuo to provide a tan solid: mp 90-95 °C (dec). ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 5.0 Hz, 1H), 7.44 (t, J = 8.6 Hz, 1H), 7.36 (d, J = 3 Hz, 1H), 7.24 (d, J = 4.9 Hz, 1H), 7.19 (m, 2H), 7.09 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.55 (s, 1H), 5.38 (bs, 1H, -OH), 4.26 (t, J = 6.2 Hz, 2H), 4.21 (t, J = 7.1 Hz, 2H), 2.60 (m, 4H), 2.36 (quintet, J = 5.8 Hz, 2H), 1.51 (hextet, J = 7.1 Hz, 2H), 1.19 (t, J = 7.5 Hz, 3H), 0.90 (t,

J = 7.4 Hz, 3H); MS FD m/e 532 (p); IR (KBr, cm^{-1}) 3200 (br), 2961, 1697, 1457, 1110. Anal. Calcd for $C_{31}H_{32}O_6S \cdot H_2O$: C, 67.62; H, 6.22. Found: C, 67.34; H, 5.87.

The cancers which may be treated using the present method, are those which are amenable to radiation therapy. These include Breast Carcinoma, Bladder Carcinoma, Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, Pediatric Malignancies and the like.

Several types of radiation are used in the treatment of cancer including X-rays gamma rays, high energy electrons and high LET (Linear Energy Transfer) radiation, such as, protons, neutron, and alpha particles. The ionizing radiation is employed by techniques well known to those skilled in the art. For example, X-rays and gamma rays are applied by external and/or interstitial means from linear accelerators or radioactive sources. High-energy electrons can be produced by linear accelerators and high LET radiation is also applied from radioactive sources implanted interstitially. The total dose of radiation employed by one skilled in the art ranges from 18 to 160 Gray (Gy). (One Gray unit of measure is equal to 100 rads) This total dose of radiation is divided into 5 to 7 continuous weeks of therapy. Typically, one week of radiation is divided into 5 daily fractions. A daily fraction of radiation consists of

a dose from 1.2 to 2.5 Gray. The total amount of radiation used in brachytherapy may be 160 Gy. The exact dosage of radiation is dependent on a variety of factors including but not limited to the volume of the cancerous tissue to be irradiated, normal tissue surrounding the cancerous tissue, age of the patient, medical history of the patient, and other clinical factors. For relevant references, see: R. Arriagada, Hematology/Oncology Clinics of North America, Vol. 11, pgs. 461-472 (1997) and S. Hellman, Principles of Cancer Management: Radiation Therapy, *in* Cancer: Principles and Practice of Oncology, 5th Ed., Lippincott Publishers, pgs. 307-332 (1997); the disclosure of which is herein incorporated by reference.

The compounds or formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I. Dosages from about 0.5 to about 300 mg/kg per

day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations of the present invention normally will consist of at least one compound selected from the compounds of Formula I and Formula II mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and

propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, injectable solutions, creams and ointments. Especially preferred are formulations for inhalation application, such as an aerosol, and for oral ingestion.

The leukotriene (LTB_4) antagonists may be administered during the course of radiation. However, it is preferred that the leukotriene (LTB_4) antagonists be administered for some time before radiation is begun. Such administration allows for an effective level of the leukotriene (LTB_4) antagonist to be established in the tissue before radiation therapy is undertaken. It is preferred to begin the administration of the leukotriene (LTB_4) antagonists 1-3 days before the beginning of the radiation therapy, and continue it throughout the course of the radiation therapy. If leukotriene (LTB_4) antagonists are administered after radiation, they should be administered within a therapeutically effective interval.

The following formulation examples illustrate the types of formulations of the leukatriene (LTB_4) antagonists which may be employed in a method of the present invention.

The examples may employ as active compounds any of the compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

FORMULATION EXAMPLE 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propanoic acid	250
Starch	200
Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

FORMULATION EXAMPLE 2

A tablet is prepared using the ingredients below:

Ingredient	Quantity (mg/capsule)
1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Magnesium stearate	5

The components are blended and compressed to form tablets each weighing 665 mg.

FORMULATION EXAMPLE 3

An aerosol solution is prepared containing the following components:

	Weight %
3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid	0.25
Ethanol	30.00
Propellant 11 (trichlorofluoromethane)	10.25
Propellant 12 (Dichlorodifluoromethane)	29.75
Propellant 114 (Dichlorotetrafluoroethane)	29.75

The active compound is dissolved in the ethanol and the solution is added to the propellant 11, cooled to -30°C. and transferred to a filling device. The required amount is then fed to a container and further filled with the pre-mixed propellants 12 and 114 by means of the cold-filled method or pressure-filled method. The valve units are then fitted to the container.

FORMULATION EXAMPLE 4

Tablets each containing 60 mg of active ingredient are made up as follows:

2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid sodium salt		60 mg
Starch		45 mg
Microcrystalline cellulose		35 mg
Polyvinylpyrrolidone (as 10% solution in water)		4 mg
Sodium carboxymethyl starch		4.5 mg
Magnesium stearate		0.5 mg
Talc		1 mg
	Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh (355 μm) U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a No. 18 mesh (1.00 mm) U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh (250 μm) U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

FORMULATION EXAMPLE 5

Capsules each containing 80 mg of medicament are made as follows:

5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-phenyl]-4-pentynoic acid	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh (355 μm) U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

FORMULATION EXAMPLE 6

Suppositories each containing 225 mg of active ingredient are made as follows:

3-(5-(6-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-1,2,3,4-tetrahydronaphthalen-1(2H)-one)propanoic acid	225 mg
Unsaturated or saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh (250 μm) U.S. sieve and suspended in the fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

FORMULATION EXAMPLE 7

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	50 mg
Sodium carboxymethyl cellulose	50 mg
Sugar	1 g
Methyl paraben	0.05 mg
Propyl paraben	0.03 mg
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh (355 μm) U.S. sieve and mixed with the sodium carboxymethylcellulose, sugar, and a portion of the water to form a suspension. The parabens, flavor and color are dissolved and diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Assay Example 1

The Nude Mouse Xenograft test used to evaluate anti-oncolytic agents of this invention is well known and

generally described in the textbook; Beverly A. Teicher, Editor, Anticancer Drug Development Guide, Humana Press, Totowa, New Jersey, 1997, p.75-124 (ISBN 0-89603-461-5); the disclosure of which is incorporated herein by reference. The xenograft test is more particularly described as follows:

Male or female nude mice, selected as appropriate to the gender of the tumor (Charles River) were treated with total body *gamma* Radiation (450 rads). After 24 hours, human LNCaP and DU-145 prostate carcinomas, human Panc-1 and BxPC-3 pancreatic carcinomas, human HT29 colon carcinoma, human MX-1 breast carcinoma (human LNCaP and DU-145 prostate carcinomas, human Panc-1 and BxPC-3 pancreatic carcinomas, human HT29 colon carcinoma carcinomas available from the American Type Culture Collection, Manassas, VA; human MX-1 breast carcinoma available from the National Cancer Institute, Bethesda, MD), prepared from a brie of donor tumors (5 x 10^6 cells), were implanted subcutaneously in a hind-leg of the mice. The mice were treated with 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (Formula IV), at a dosage of 30, 100, or 200, mg per kilogram daily, administered orally, beginning 4 days after the tumor cell implantation. The mice were then treated with *gamma* radiation locally at the tumor-bearing limb at exposures of 200, 300, or 400 rads per fraction to total doses of 1000, 1500, or 2000 rads in five fractions or to total doses of 2000, 3000, or 4000 rads in ten fractions.

Tumor response was monitored by tumor volume measurement performed twice per week over the course of 60-90 days. Body weights were determined as a general measurement of toxicity. The mice were divided into an

untreated control group and multiple treatment groups with five mice in each group.

The data was analyzed by determining the mean tumor volume for the control group and each treatment group over the course of the experiment. The tumor growth delay was calculated as the difference in days for the treatment versus the control tumors to reach the volume of 1000 mm^3.

Assay Example 2

The murine Lewis lung carcinoma was implanted in male C57Bl mice and the tumor-bearing animals were treated with the compound of Formula IV alone or along with fractionated radiation therapy. Specifically, Lewis lung tumor cells prepared from a brie of donor tumors (1×10^6 cells) were implanted subcutaneously in a hind-leg of male C57Bl mice (Charles River). Fractionated radiation therapy was delivered locally to the tumor-bearing limb in fractions of 200, 300, or 400 rads (GammaCell 40 irradiator, MSD Nordion Inc., Ottawa, ON, Canada, 137 cesium source) once per day on days 7 through 11 post tumor cell implantation. This radiation was administered alone or along with the compound of Formula IV. Treatment with the compound of Formula IV (100 mg/kg) was administered orally on day 4 post tumor cell implantation and continued daily until day 21.

Each treatment group as well as a group of untreated control animals consisted of five animals per group. Tumor response was monitored by tumor volume measurement performed twice per week over the course of 31 days. Lung metastases were counted from two animals per group. Body weights were determined as a general measure of toxicity.

The data was analyzed by determining the mean tumor volume for each treatment group over the course of the experiment and calculating the tumor growth delay as the difference in days for the treatment versus the control tumors to reach a volume of 500 mm^3.

Table 1

Mouse Xenograft Test Results

Growth Delay of Prostate Tumor(1)

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Formula IV	30	-	5.8	0.5
Formula IV	100	-	7.7	0.6
Radiation	-	200	11.3	1.0
Radiation	-	300	15.3	1.4
Radiation	-	400	19.2	1.8
Formula IV + Radiation	30	200	15.3	1.4
Formula IV + Radiation	30	300	20.6	2.0
Formula IV + Radiation	30	400	26.4	2.4
Formula IV + Radiation	100	200	20.2	1.8
Formula IV + Radiation	100	300	25.0	2.3
Formula IV + Radiation	100	400	31.5	3.0

(1) = Human DU145 prostate carcinoma

Formula IV = the LTB_4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid

Radiation = ten fractions of dose Rads from a GammaCell 40 irradiator, MSD Nordion, Inc.

Dose Formula IV = milligrams per kilogram mouse body weight

Dose Rads = rads per fraction

Rads = 0.01 gray = 0.01 joule per kilogram

TGD = average tumor growth delay in days

sem = standard error of the mean

Table 2

Mouse Xenograft Test Results

Growth Delay of Prostate Tumor[(2)]

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Formula IV	30	-	1.2	0.3
Formula IV	100	-	2.0	0.3
Formula IV	200	-	2.2	0.3
Radiation	-	300	18.1	1.3
Formula IV + Radiation	100	300	26.3	2.0

(2) = Human LNCaP prostate carcinoma

Table 3

Mouse Xenograft Test Results

Growth Delay of Colon Tumor[3]

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Formula IV	30	-	5.0	0.3
Formula IV	100	-	13.0	1.1
Formula IV	200	-	15.2	1.2
Radiation	-	300	19.2	2.0
Formula IV + Radiation	100	300	27.8	3.0

(3) = Human HT29 Colon carcinoma

Table 4

Mouse Xenograft Test Results

Growth Delay of Pancreatic Tumor[4]

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Formula IV	30	-	10.2	1.4
Formula IV	100	-	16.7	2.0
Formula IV	200	-	19.4	2.4
Radiation	-	300	27.1	3.2
Formula IV + Radiation	100	300	50.5	5.5

(4) = Human Panc-1 pancreatic carcinoma

Table 5

Mouse Xenograft Test Results

Growth Delay of Pancreatic Tumor(5)

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Formula IV	30	-	7.4	0.5
Formula IV	100	-	21.6	2.0
Radiation	-	200	25.6	2.4
Radiation	-	300	32.6	3.0
Radiation	-	400	38.0	3.5
Formula IV + Radiation	30	200	30.0	2.6
Formula IV + Radiation	30	300	37.3	3.3
Formula IV + Radiation	30	400	41.6	3.8
Formula IV + Radiation	100	200	34.0	3.1
Formula IV + Radiation	100	300	40.8	3.6
Formula IV + Radiation	100	400	51.4	4.7

(5) = Human BxPC3 Pancreatic Carcinoma

Table 6

Mouse Xenograft Test Results

Growth Delay of Breast Tumor[6]

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Radiation	-	200	11.7	1.2
Radiation	-	300	14.5	1.5
Radiation	-	400	15.6	1.6
Formula IV	100	-	6.2	0.4
Formula IV + Radiation	100	200	12.4	1.1
Formula IV + Radiation	100	300	16.3	1.6
Formula IV + Radiation	100	400	26.8	2.5

(6) = Human MX-1 breast carcinoma

Table 7

Lewis Lung Test Results

Growth Delay of Lung Tumor(7)

Treatment	dose Formula IV	dose Rads	TGD	TGD sem
Radiation	-	200	4.4	0.3
Radiation	-	300	7.5	0.6
Radiation	-	400	9.6	1.0
Formula IV	100	-	1.7	0.3
Formula IV + Radiation	100	200	9.9	1.0
Formula IV + Radiation	100	300	11.3	1.1
Formula IV + Radiation	100	400	13.6	1.3

(7) = Primary Lewis lung carcinoma

Radiation = five fractions of dose Rads from a GammaCell 40 irradiator, MSD Nordion, Inc.

Table 8
Lewis Lung Test Results
Reduction in Mean Number of Lung Metastases

Treatment	dose Formula IV	dose Rads	MNLM
Radiation	-	200	20.5
Radiation	-	300	16.5
Radiation	-	400	15.5
Formula IV	100	-	20.0
Formula IV + Radiation	100	200	14.0
Formula IV + Radiation	100	300	13.0
Formula IV + Radiation	100	400	12.0

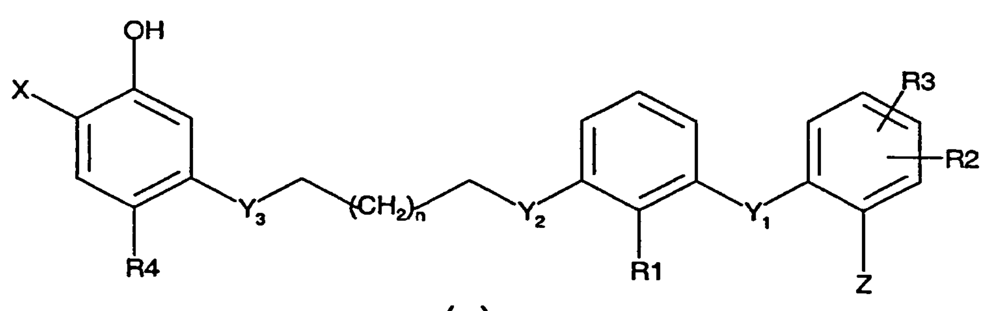
MNLM = Mean number of lung metastases
Radiation = five fractions of dose Rads from a GammaCell 40 irradiator, MSD Nordion, Inc.

What is claimed is:

1. A method of treating a human patient suffering from cancer which comprises administering to said patient ionizing radiation in conjunction with an effective amount of a leukotriene LTB_4 inhibitor selected from the group consisting of Formula A, Formula I and Formula II or a pharmaceutically acceptable base addition salt thereof.

2. Use of an LTB_4 antagonist for the manufacture of a medicament for administration in combination with irradiation with high energy radiation for the treatment of cancer.

3. The use according to claim 2 wherein the leukotriene (LTB_4) antagonist is represented by the formula (I)



(I)

wherein:

X is selected from the group consisting of,

(i) a five membered substituted or unsubstituted heterocyclic radical containing from 1 to 4 hetero atoms independently selected from sulfur, nitrogen or oxygen; and

(ii) a fused bicyclic radical wherein a carbocyclic group is fused to two adjacent carbon atoms of the five membered heterocyclic radical, (i);

Y_1 is a bond or divalent linking group containing 1 to 9 atoms;

Y_2 and Y_3 are divalent linking groups independently selected from $-CH_2-$, -O-, or -S-;

Z is an Acidic Group;

R1 is C_1-C_{10} alkyl, aryl, C_3-C_8 cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6-C_{20} aralkyl, C_6-C_{20} alkaryl, C_1-C_{10} haloalkyl, C_6-C_{20} aryloxy, or C_1-C_{10} alkoxy;
R2 is hydrogen, halogen, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, Acidic Group, or $-(CH_2)_{1-7}$-(Acidic Group);

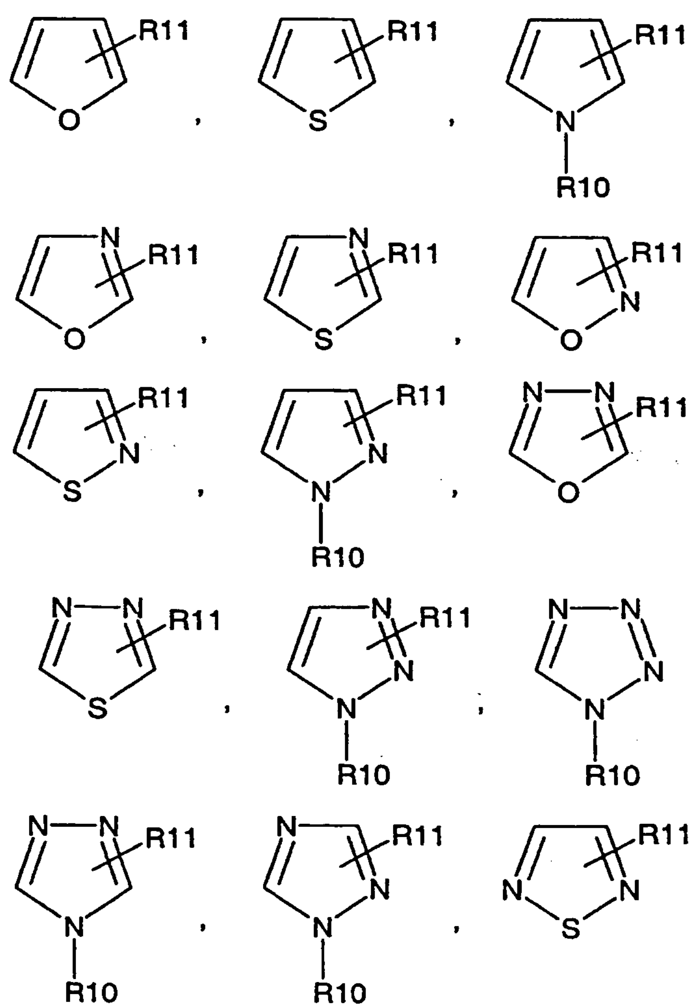
R3 is hydrogen, halogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_6-C_{20} aryloxy, or C_3-C_8 cycloalkyl;

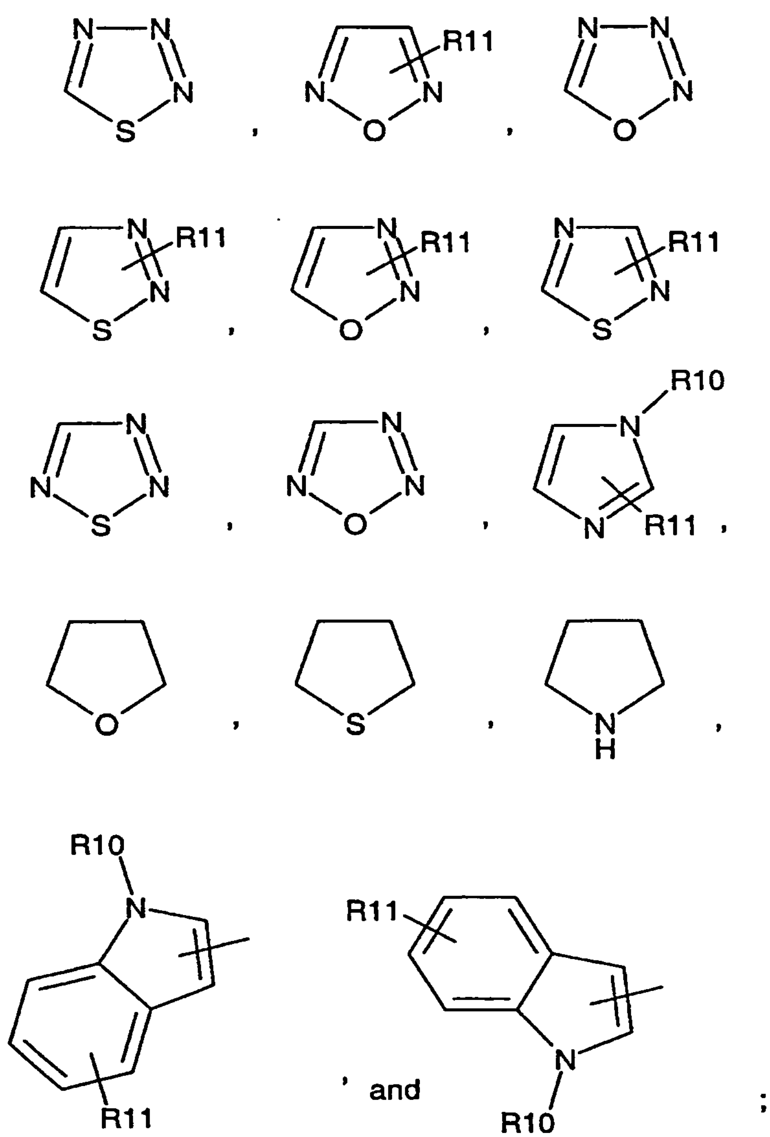
R4 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl, $-(CH_2)_{1-7}-(C_3$-C_4 cycloalkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, benzyl, or aryl; and

n is 0, 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof.

4. The use of claim 3 wherein X is a heterocyclic radical selected from the group consisting of substituents represented by the following formulae:





where R10 is a radical selected from hydrogen or C_1-C_4 alkyl; and R11 is a radical selected from hydrogen, halo, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, aryl, or C_6-C_{20} aryloxy.

5. The use according to claim 4 wherein the R1, R2, R3 and R4 groups for substitution in formula (I) are selected from the following variables coded R01 thru R16

R variables Combination Code	R1 group choice	R2 group choice	R3 group choice	R4 group choice
R01	R1	R2	R3	R4
R02	R1	R2	R3	PG1-R4
R03	R1	R2	PG1-R3	R4
R04	R1	R2	PG1-R3	PG1-R4
R05	R1	PG1-R2	R3	R4
R06	R1	PG1-R2	R3	PG1-R4
R07	R1	PG1-R2	PG1-R3	R4
R08	R1	PG1-R2	PG1-R3	PG1-R4
R09	PG1-R1	R2	R3	R4
R10	PG1-01	R2	R3	PG1-R4
R11	PG1-R1	R2	PG1-R3	R4
R12	PG1-R1	R2	PG1-R3	PG1-R4
R13	PG1-R1	PG1-R2	R3	R4
R14	PG1-R1	PG1-R2	R3	PG1-R4
R15	PG1-R1	PG1-R2	PG1-R3	R4
R16	PG1-R1	PG1-R2	PG1-R3	PG1-R4

and;

the Y1, Y2, and Y3 groups for substitution in formula (I) are selected from the following variables coded Y01 thru Y27:

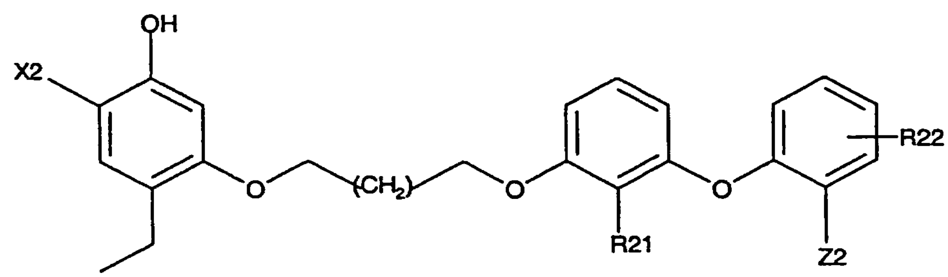
Y variables combination code	Y1 group choice	Y2 group choice	Y3 group choice
Y01	Y1	Y2	Y3
Y02	Y1	Y2	PG1-Y3
Y03	Y1	Y2	PG2-Y3
Y04	Y1	PG1-Y2	Y3
Y05	Y1	PG2-Y2	Y3
Y06	Y1	PG1-Y2	PG1-Y3
Y07	Y1	PG1-Y2	PG2-Y3
Y08	Y1	PG2-Y2	PG1-Y3
Y09	Y1	PG2-Y2	PG2-Y3
Y10	PG1-Y1	Y2	Y3
Y11	PG1-Y1	Y2	PG1-Y3
Y12	PG1-Y1	Y2	PG2-Y3
Y13	PG1-Y1	PG1-Y2	Y3
Y14	PG1-Y1	PG1-Y2	PG1-Y3
Y15	PG1-Y1	PG1-Y2	PG2-Y3
Y16	PG1-Y1	PG2-Y2	Y3
Y17	PG1-Y1	PG2-Y2	PG1-Y3
Y18	PG1-Y1	PG2-Y2	PG2-Y3
Y19	PG2-Y1	Y2	Y3
Y20	PG2-Y1	Y2	PG1-Y3
Y21	PG2-Y1	Y2	PG2-Y3
Y22	PG2-Y1	PG1-Y2	Y3
Y23	PG2-Y1	PG1-Y2	PG1-Y3
Y24	PG2-Y1	PG1-Y2	PG2-Y3
Y25	PG2-Y1	PG2-Y2	Y3
Y26	PG2-Y1	PG2-Y2	PG1-Y3
Y27	PG2-Y1	PG2-Y2	PG2-Y3

and;

the X and Z groups and the n variable for substitution in formula (I) are selected from the following variables coded XZn01 thru XZn24:

XZn variables combination code	X group choice	Z Group Choice	n integer group choice
XZn01	X	Z	n
XZn02	X	Z	PG1-n
XZn03	X	Z	PG2-n
XZn04	X	PG1-Z	n
XZn05	X	PG2-Z	n
XZn06	X	PG3-Z	n
XZn07	X	PG1-Z	PG1-n
XZn08	X	PG2-Z	PG1-n
XZn09	X	PG3-Z	PG1-n
XZn10	X	PG1-Z	PG2-n
XZn11	X	PG2-Z	PG2-n
XZn12	X	PG3-Z	PG2-n
XZn13	PG1-X	Z	n
XZn14	PG1-X	Z	PG1-n
XZn15	PG1-X	Z	PG2-n
XZn16	PG1-X	PG1-Z	n
XZn17	PG1-X	PG2-Z	n
XZn18	PG1-X	PG3-Z	n
XZn19	PG2-X	PG1-Z	PG1-n
XZn20	PG2-X	PG2-Z	PG1-n
XZn21	PG2-X	PG3-Z	PG1-n
XZn22	PG2-X	PG1-Z	PG2-n
XZn23	PG2-X	PG2-Z	PG2-n
XZn24	PG2-X	PG3-Z	PG2-n

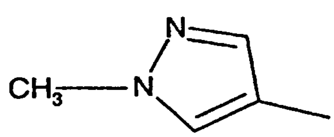
6. The use according to claim 3 wherein the leukotriene B4 antagonist is described by formula (II):



(II)

wherein;

X2 is a heterocyclic radical selected from,



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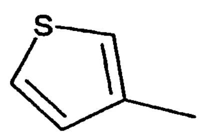

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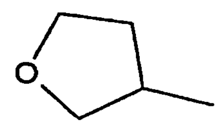

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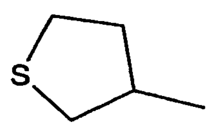


;

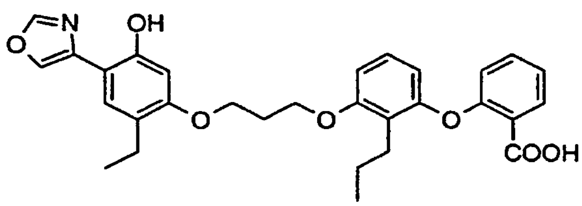
R21 is ethyl, 2-propen-1-yl, 3-propen-1-yl, n-propyl, iso-propyl, n-butyl, sec-butyl, or tert-butyl; and

R22 is hydrogen, n-butyl, sec-butyl, fluoro, chloro, $-CF_3$, or tert-butyl.

Z2 is the Acidic Group selected from carboxyl, tetrazolyl, or N-sulfonamidyl;

or a salt, solvate or prodrug thereof.

7. The use according to claim 6 wherein the leukotriene antagonist is a compound selected from the following:



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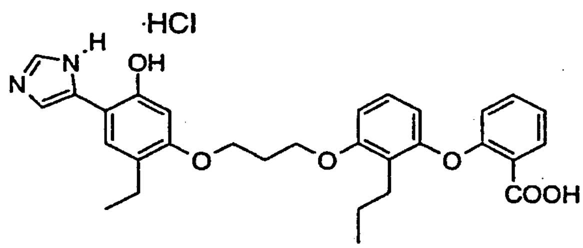

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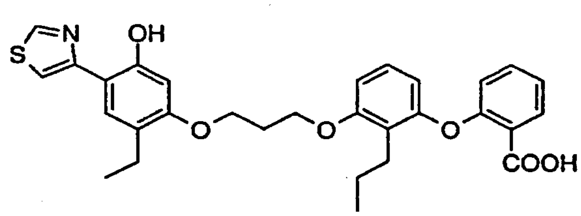

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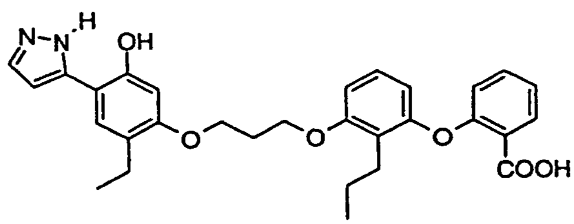

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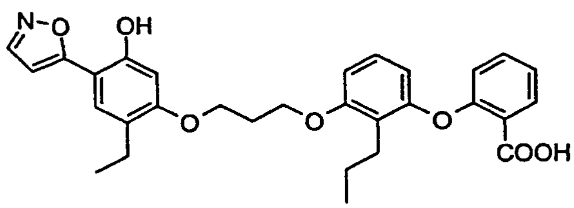

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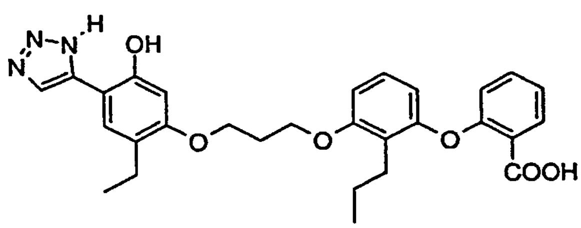

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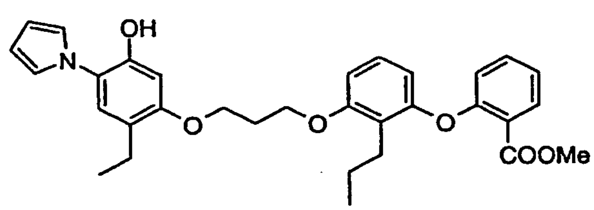

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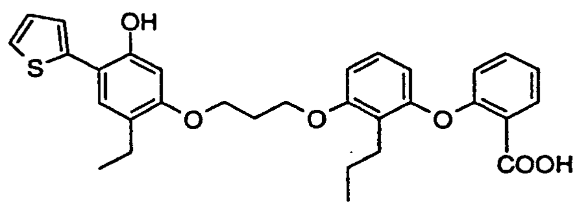

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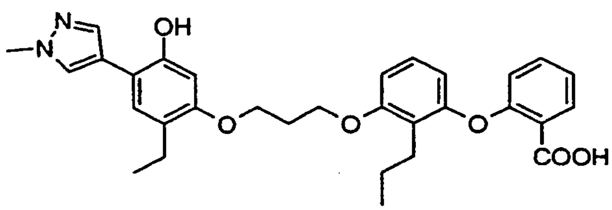

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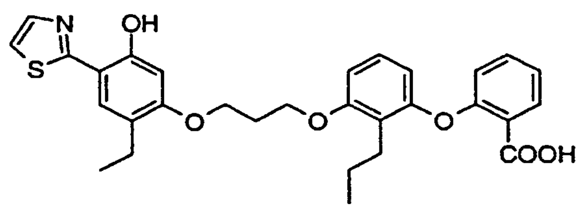

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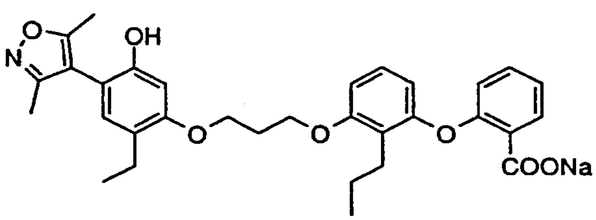

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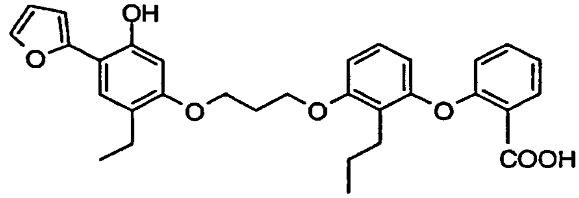

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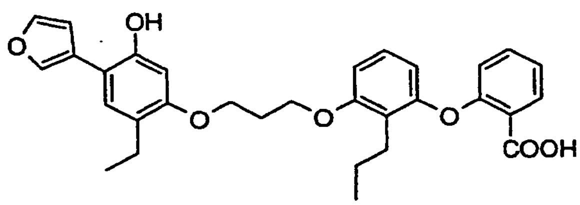

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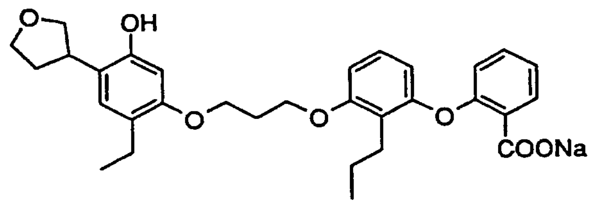

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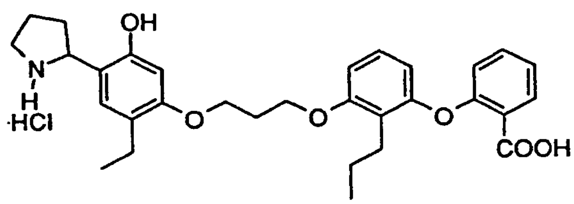

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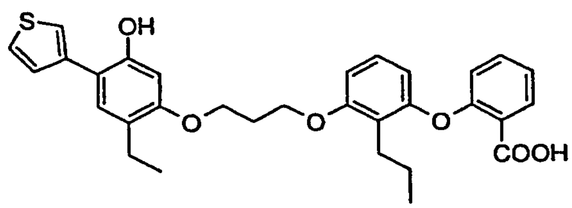

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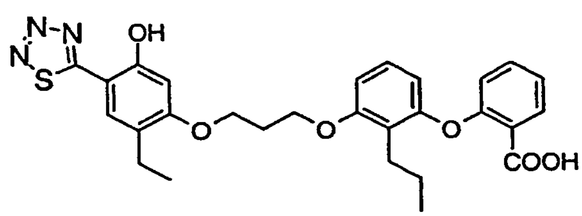

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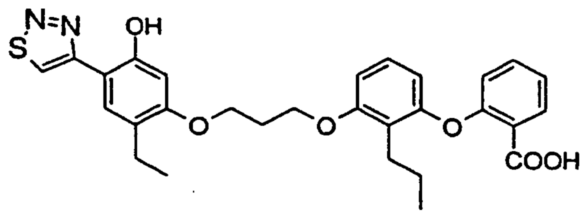

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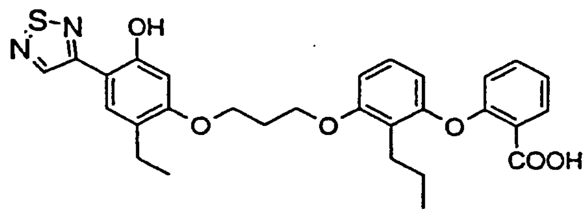

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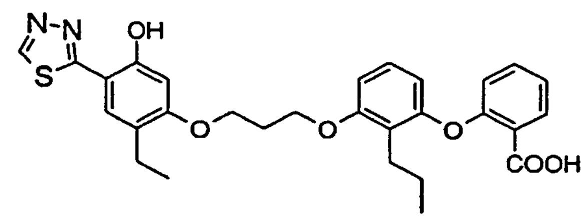

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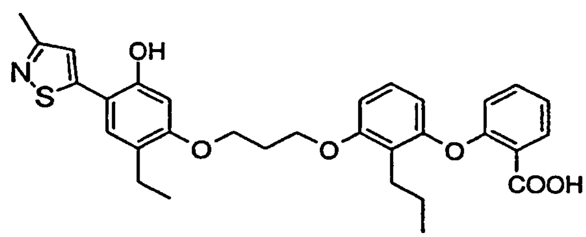

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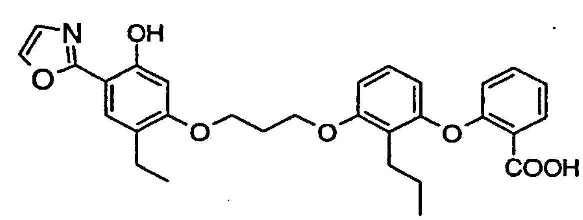

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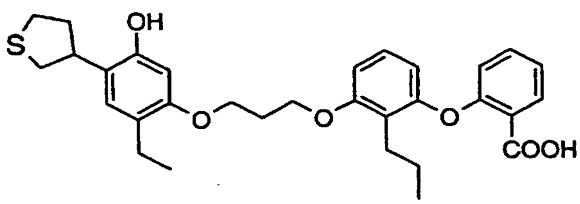

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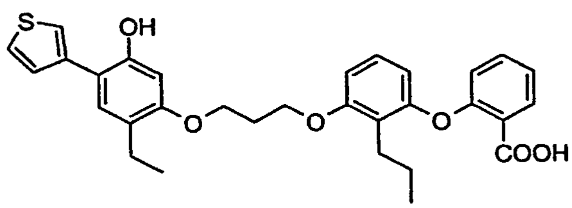
or an acid, salt, solvate or prodrug derivative thereof.

8. The use according to claim 7 wherein the leukotriene antagonist is a compound selected from the following:



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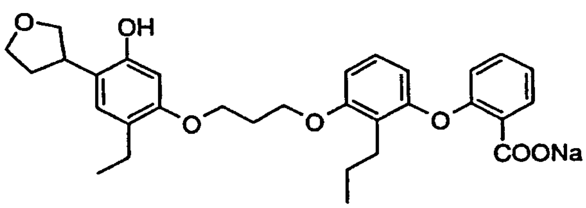

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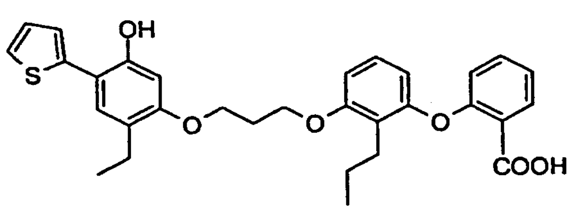

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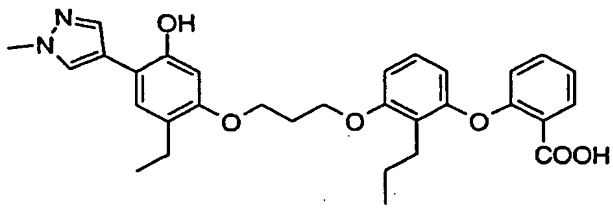

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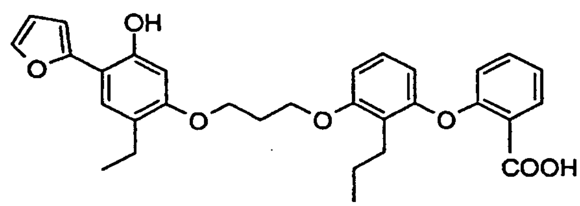

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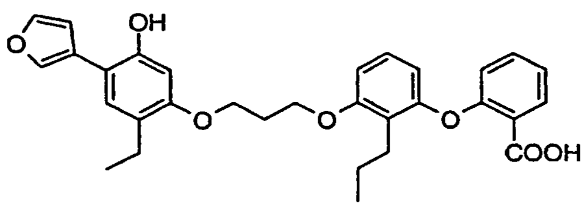

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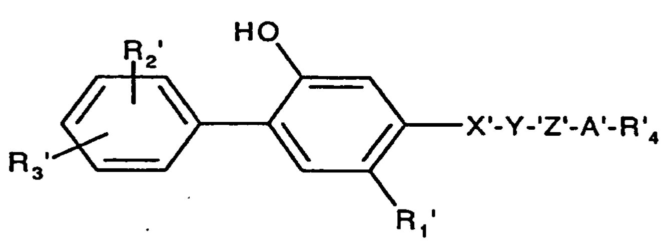
or an acid, salt, solvate or prodrug derivative thereof.

9. The use according to claim 2 wherein the leukotriene (LTB4) antagonist is represented by a compound of the structure (Formula A):



Formula A

or a pharmaceutically acceptable base addition salt thereof, wherein:

$R_{1'}$ is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substitutedphenyl;

each $R_{2'}$ and $R_{3'}$ are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-(O)$_q$ S-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X' is -O-, -S-, -C(=O), or -CH_2-;

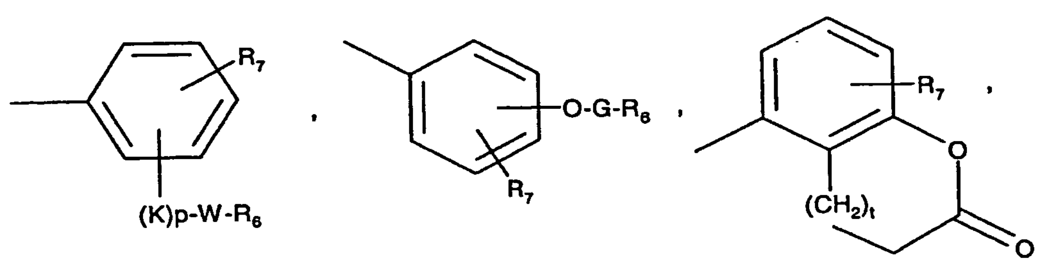
Y' is -O- or -CH_2-;

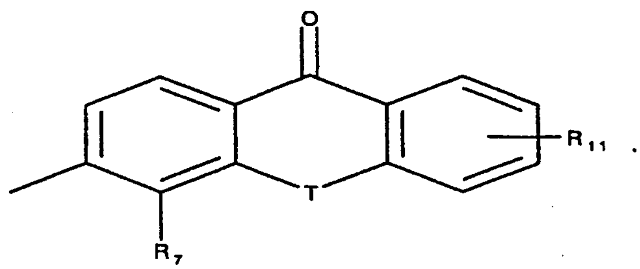
or when taken together, -X'-Y'- is -CH=CH- or -C/C-;

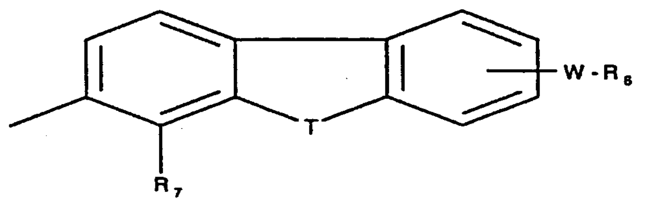
Z' is a straight or branched chain C_1-C_{10} alkylidenyl;

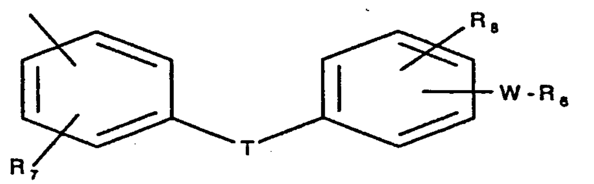
A' is a bond, -O-, -S-, -CH=CH-, or -CR_aR_b-, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

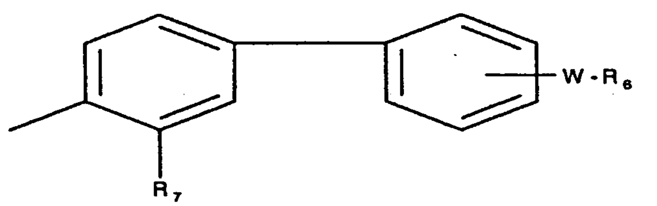
$R_{4'}$ is R_6, or represented by one of the following formulae:











wherein:

each R_6 is independently -COOH, 5-tetrazolyl, -CON$(R_9)_2$, or -CONHSO$_2$R$_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, -W-R_6, -T-G-R_6, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, $-W-R_6$, or $-T-G-R_6$;

each W is a bond or a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $(O)_q$ S-;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

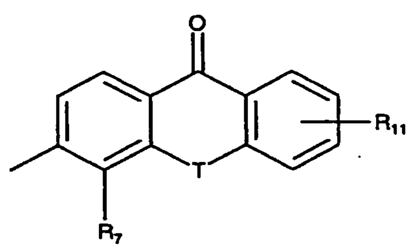
provided when X is -O- or -S-, Y is not -O-;

provided when A is -O- or -S-, R_4 is not R_6;

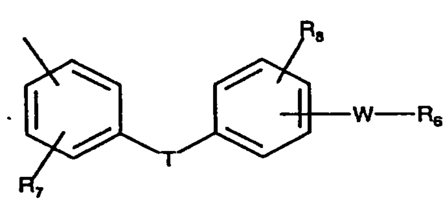
and provided W is not a bond when p is 0;

and the pharmaceutically-acceptable salts thereof.

10. The use according to claim 9 wherein R4'is selected from the following formulae:

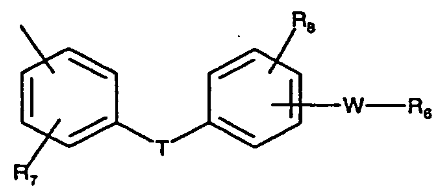


, or



.

11. The use according to claim 10 wherein R4'is:



13. The use according to claim 12 wherein said compound is selected from the group (A) to (KKKK) consisting of:

A) 2-Methyl-2-(1H-tetrazol-5-yl)-7-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)heptane;

B) 2-Methyl-2-(1H-tetrazol-5-yl)-7-(2-ethyl-4-(3-fluorophenyl)-5-hydroxyphenoxy)heptane;

C) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-dimethylaminocarbonylbutyloxy)phenyl) propionic acid;

D) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

E) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxybutyloxy)phenyl)propionic acid;

F) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-methoxyphenyl)propionic acid;

G) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-(1H-tetrazol-5-yl)butyloxy)phenyl)propionic acid;

H) Methyl 3-(2-(4-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)-(1-butenyl))phenyl)propionate;

I) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)-(1-butenyl))phenyl)propionic acid;

J) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyl)phenyl)propionic acid;

K) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyl)-6-methoxyphenyl)propionic acid;

L) Methyl 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-hydroxyphenyl)propionate;

M) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-hydroxyphenyl)propionic acid;

N) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-butyloxy)phenyl)propionic acid;

O) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-methylthiobutyloxy)phenyl)propionic acid;

P) 3-(2-(3-(2,4-Di-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxybutoxy)phenyl)propionic acid;

Q) 6-Methyl-6-(1H-tetrazol-5-yl)-11-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)undecane;

R) N,N-Dimethyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

S) N-Methanesulfonyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

T) N-Phenylsulfonyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

U) 3-(2-(3-(2-Butyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

V) Ethyl 3-(2-(4-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyloxy)phenyl)propionate;

W) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyloxy)phenyl)propionic acid;

X) Methyl 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-(methoxycarbonyl)phenoxy)phenyl)propionate;

Y) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propionic acid;

Z) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-4-(4-carboxyphenoxy)phenyl)propionic acid;

AA) 3,3-Dimethyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

BB) 2-Methyl-2-(1H-tetrazol-5-yl)-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propane;

CC) 2-Methyl-2-(1H-tetrazol-5-yl)-3-hydroxy-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propane;

DD) 3-(2-(3-(2-Bromo-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

EE) 3-(2-(3-(2-Ethylthio-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

FF) Methyl 3-(2-hydroxy-3-(4-methoxycarbonylbutyl)-6-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionate;

GG) 5-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-8-(4-carboxybutyl)dihydrocoumarin;

HH) 2-Phenyl-4-ethyl-5-[6-(2H-tetrazol-5-yl)-6-methylheptyloxy]phenol sodium salt;

II) 2-(4-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

JJ) 2-(3-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

KK) 2-(2-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

LL) 2-(4-Methoxyphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

MM) 2-(3-Methoxyphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

NN) 2-(4-Trifluoromethylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

OO) 2-(3-Dimethylaminophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

PP) 3-(5-(6-(4-Phenyl-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-1,2,3,4 -tetrahydronaphthalen-1(2H)-one)propanoic acid;

QQ) 3-(5-(6-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-

1,2,3,4-tetrahydronaphthalen-1(2H)-one)propanoic acid;

RR) 3-(4-(5-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-2,3-dihydroinden-1(2H)-one)propanoic acid;

SS) 3,3-Dimethyl-5-(3-(2-carboxyethyl)-4-(3-(4-fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)phenyl)-5-oxopentanoic acid;

TT) 7-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

UU) 8-Propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

VV) 2-[3-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]propanoic acid;

WW) 2-(4-Chlorophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol monosodium salt;

XX) 2-(3,5-Dichlorophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol monosodium salt;

YY) 3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt;

ZZ) 7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate;

AAA) 2-[2-Propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid sodium salt hemihydrate;

BBB) 3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy][1,1'-biphenyl]-4-propanoic acid disodium salt monohydrate;

CCC) 5-Ethyl-4-[3-[2-propyl-3-[2-(2H-tetrazol-5-yl)phenoxy]phenoxy]propoxy][1,1'-biphenyl]-2-ol disodium salt sesquihydrate;

DDD) 3-[4-[3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9-oxo-9H-xanthene]]propanoic acid sodium salt hemihydrate;

EEE) 2-Fluoro-6-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid disodium salt;

FFF) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt;

GGG) 3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]] propanoic acid disodium salt trihydrate;

HHH) 3-[4-[9-Oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid;

III) 3-[2-[1-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-4-(5-oxo-5-morpholinopentanamido)phenyl]propanoic acid;

JJJ) 2-Fluoro-6-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid disodium salt hydrate;

KKK) 4-Fluoro-2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

LLL) 2-[2-Propyl-3-[5-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]pentoxy]phenoxy]benzoic acid;

MMM) 2-[2-Propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]butoxy]phenoxy]benzoic acid sesquihydrate;

NNN) 2-[2-(2-Methylpropyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

OOO) 2-[2-Butyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid hydrate;

PPP) 2-[2-(Phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

QQQ) 2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]phenylacetic acid;

RRR) 2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid;

SSS) 2-[[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl]benzoic acid;

TTT) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid;

UUU) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfinyl]benzoic acid;

VVV) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfonyl]benzoic acid hydrate;

WWW) 5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-

hydroxyphenoxy]propoxy]phenyl]-4-pentynoic acid disodium salt 0.4 hydrate;

XXX) 1-Phenyl-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

YYY) 1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

ZZZ) 1-(4-(Dimethylaminocarbonylmethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

AAAA) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)-E-propenoic acid;

BBBB) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)-2-methyl-E-propenoic acid;

CCCC) 5-(2-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)ethyl)-1H-tetrazole;

DDDD) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-4-(4-carboxybutyloxy)phenyl)propionic acid;

EEEE) 5-[3-[4-(4-Fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-one;

FFFF) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}phenyl)propanoic acid;

GGGG) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-4-propylphenyl)propanoic acid sodium salt;

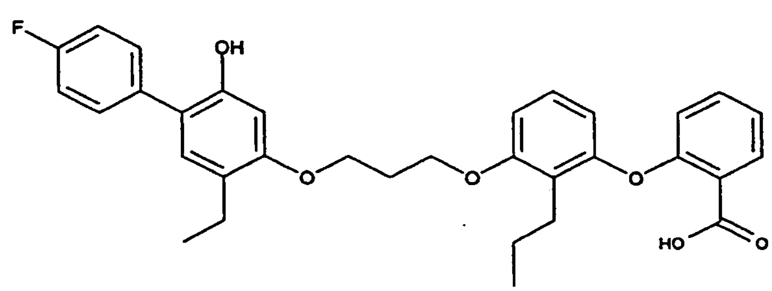
HHHH) 3-(4-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-3-propylphenyl)propanoic acid;

IIII) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-2-propylphenyl)propanoic acid;

JJJJ) 3-{3-[3-(2-Ethyl-5-hydroxyphenyloxy)propoxy]-2-propylphenyl}propanoic acid disodium salt; and

KKKK) 2-[3-[3-[2-Ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid disodium salt hemihydrate.

14. The use according to claim 12 wherein the leukotriene (LTB_4) antagonist is a compound of the structure (Formula B):



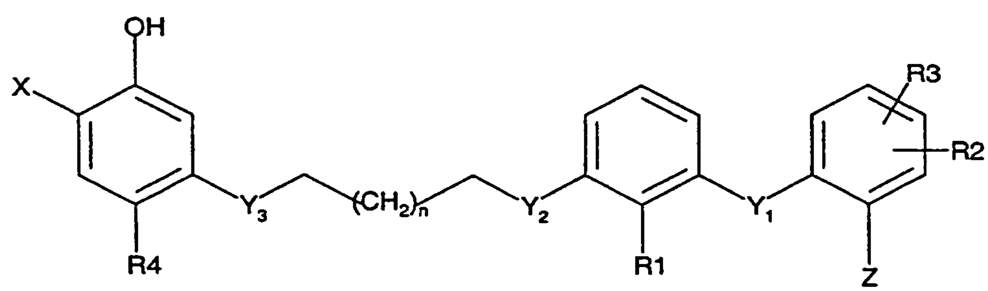
Formula B

namely, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxybenzoic acid, and the pharmaceutically acceptable salts thereof.

15. A method of treating cancer in a mammalian patient comprising administering to said patient a therapeutically effective amount of a leukotriene (LTB_4)

antagonist in combination with irradiation with high energy radiation.

16. The method of claim 15 wherein the leukotriene (LTB4) antagonist is represented by the formula (I)



(I)

wherein:

X is selected from the group consisting of,

(i) a five membered substituted or unsubstituted heterocyclic radical containing from 1 to 4 hetero atoms independently selected from sulfur, nitrogen or oxygen; and

(ii) a fused bicyclic radical wherein a carbocyclic group is fused to two adjacent carbon atoms of the five membered heterocyclic radical, (i);

Y_1 is a bond or divalent linking group containing 1 to 9 atoms;

Y_2 and Y_3 are divalent linking groups independently selected from $-CH_2-$, -O-, or -S-;

Z is an Acidic Group;

R1 is C_1-C_{10} alkyl, aryl, C_3-C_8 cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6-C_{20} aralkyl, C_6-C_{20} alkaryl, C_1-C_{10} haloalkyl, C_6-C_{20} aryloxy, or C_1-C_{10} alkoxy;
R2 is hydrogen, halogen, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, Acidic Group, or $-(CH_2)_{1-7}$-(Acidic Group);

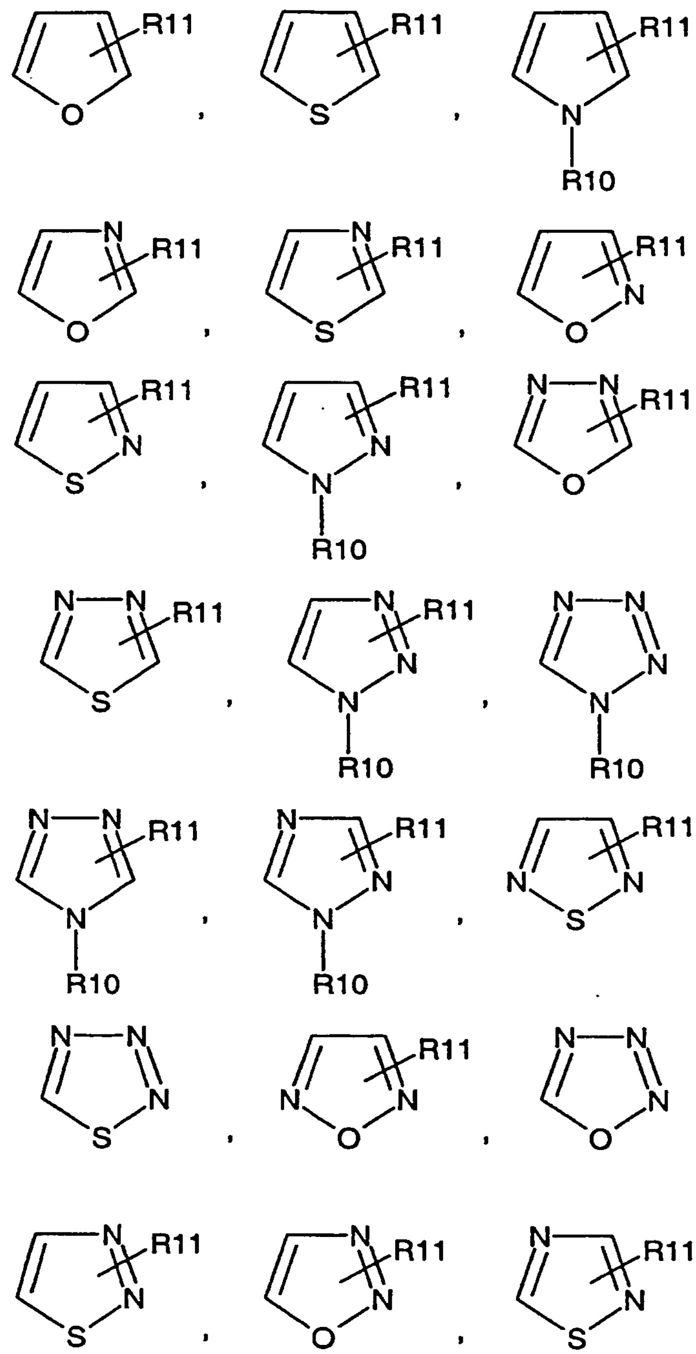
R3 is hydrogen, halogen, C_1-C_{10} alkyl, aryl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_6-C_{20} aryloxy, or C_3-C_8 cycloalkyl;

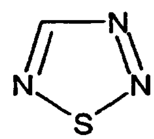
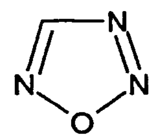
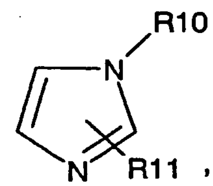
R4 is C_1-C_4 alkyl, C_3-C_4 cycloalkyl, $-(CH_2)_{1-7}-(C_3$-C_4 cycloalkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, benzyl, or aryl; and

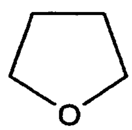
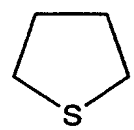
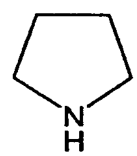
n is 0, 1, 2, 3, 4, 5, or 6;

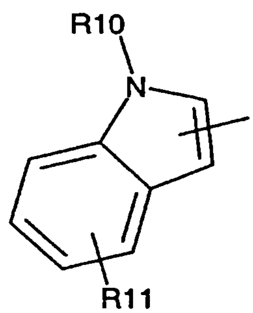
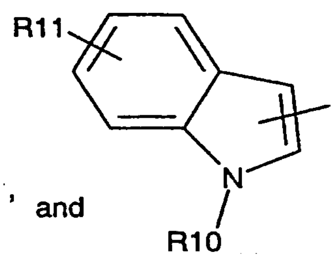
or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof.

17. The method according to claim 16 wherein X is a heterocyclic radical selected from the group consisting of substituents represented by the following formulae:


R11
O
S
N
R10

 ,  ,  ,

 ,  ,  ,

 , and  ;

where R10 is a radical selected from hydrogen or C_1-C_4 alkyl; and R11 is a radical selected from hydrogen, halo, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, aryl, or C_6-C_{20} aryloxy.

18. The method according to claim 17 wherein the R1, R2, R3 and R4 groups for substitution in formula (I) are selected from the following variables coded R01 thru R16

R variables Combination Code	R1 group choice	R2 group choice	R3 group choice	R4 group choice
R01	R1	R2	R3	R4
R02	R1	R2	R3	PG1-R4
R03	R1	R2	PG1-R3	R4
R04	R1	R2	PG1-R3	PG1-R4
R05	R1	PG1-R2	R3	R4
R06	R1	PG1-R2	R3	PG1-R4
R07	R1	PG1-R2	PG1-R3	R4
R08	R1	PG1-R2	PG1-R3	PG1-R4
R09	PG1-R1	R2	R3	R4
R10	PG1-01	R2	R3	PG1-R4
R11	PG1-R1	R2	PG1-R3	R4
R12	PG1-R1	R2	PG1-R3	PG1-R4
R13	PG1-R1	PG1-R2	R3	R4
R14	PG1-R1	PG1-R2	R3	PG1-R4
R15	PG1-R1	PG1-R2	PG1-R3	R4
R16	PG1-R1	PG1-R2	PG1-R3	PG1-R4

and;

the Y1, Y2, and Y3 groups for substitution in formula (I) are selected from the following variables coded Y01 thru Y27:

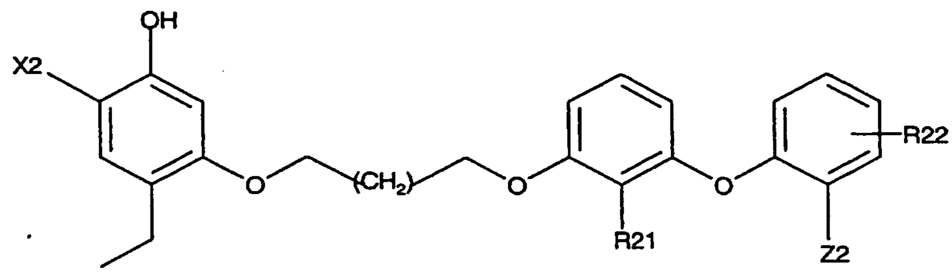
Y variables combination code	Y1 group choice	Y2 group choice	Y3 group choice
Y01	Y1	Y2	Y3
Y02	Y1	Y2	PG1-Y3
Y03	Y1	Y2	PG2-Y3
Y04	Y1	PG1-Y2	Y3
Y05	Y1	PG2-Y2	Y3
Y06	Y1	PG1-Y2	PG1-Y3
Y07	Y1	PG1-Y2	PG2-Y3
Y08	Y1	PG2-Y2	PG1-Y3
Y09	Y1	PG2-Y2	PG2-Y3
Y10	PG1-Y1	Y2	Y3
Y11	PG1-Y1	Y2	PG1-Y3
Y12	PG1-Y1	Y2	PG2-Y3
Y13	PG1-Y1	PG1-Y2	Y3
Y14	PG1-Y1	PG1-Y2	PG1-Y3
Y15	PG1-Y1	PG1-Y2	PG2-Y3
Y16	PG1-Y1	PG2-Y2	Y3
Y17	PG1-Y1	PG2-Y2	PG1-Y3
Y18	PG1-Y1	PG2-Y2	PG2-Y3
Y19	PG2-Y1	Y2	Y3
Y20	PG2-Y1	Y2	PG1-Y3
Y21	PG2-Y1	Y2	PG2-Y3
Y22	PG2-Y1	PG1-Y2	Y3
Y23	PG2-Y1	PG1-Y2	PG1-Y3
Y24	PG2-Y1	PG1-Y2	PG2-Y3
Y25	PG2-Y1	PG2-Y2	Y3
Y26	PG2-Y1	PG2-Y2	PG1-Y3
Y27	PG2-Y1	PG2-Y2	PG2-Y3

and;

the X and Z groups and the n variable for substitution in formula (I) are selected from the following variables coded XZn01 thru XZn24:

XZn variables combination code	X group choice	Z Group Choice	n integer group choice
XZn01	X	Z	n
XZn02	X	Z	PG1-n
XZn03	X	Z	PG2-n
XZn04	X	PG1-Z	n
XZn05	X	PG2-Z	n
XZn06	X	PG3-Z	n
XZn07	X	PG1-Z	PG1-n
XZn08	X	PG2-Z	PG1-n
XZn09	X	PG3-Z	PG1-n
XZn10	X	PG1-Z	PG2-n
XZn11	X	PG2-Z	PG2-n
XZn12	X	PG3-Z	PG2-n
XZn13	PG1-X	Z	n
XZn14	PG1-X	Z	PG1-n
XZn15	PG1-X	Z	PG2-n
XZn16	PG1-X	PG1-Z	n
XZn17	PG1-X	PG2-Z	n
XZn18	PG1-X	PG3-Z	n
XZn19	PG2-X	PG1-Z	PG1-n
XZn20	PG2-X	PG2-Z	PG1-n
XZn21	PG2-X	PG3-Z	PG1-n
XZn22	PG2-X	PG1-Z	PG2-n
XZn23	PG2-X	PG2-Z	PG2-n
XZn24	PG2-X	PG3-Z	PG2-n

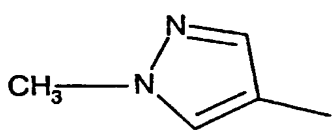
19. A method according to claim 16 wherein the leukotriene B4 antagonist is described by formula (II):

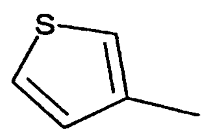


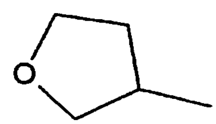
(II)

wherein;

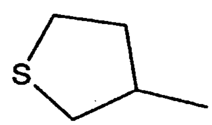
X2 is a heterocyclic radical selected from,







, , , or



;

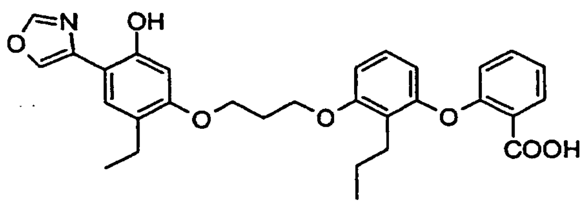
R21 is ethyl, 2-propen-1-yl, 3-propen-1-yl, n-propyl, iso-propyl, n-butyl, sec-butyl, or tert-butyl; and

R22 is hydrogen, n-butyl, sec-butyl, fluoro, chloro, $-CF_3$, or tert-butyl.

Z2 is the Acidic Group selected from carboxyl, tetrazolyl, or N-sulfonamidyl;

or a salt, solvate or prodrug thereof.

20. The method according to claim 19, wherein the leukotriene antagonist is a compound selected from the following:



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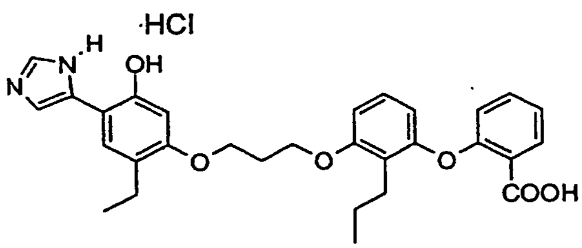

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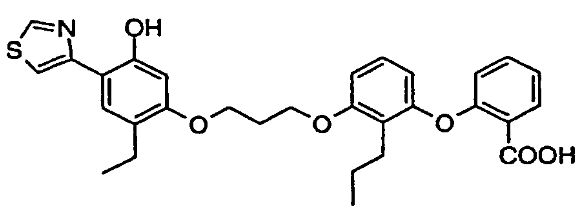

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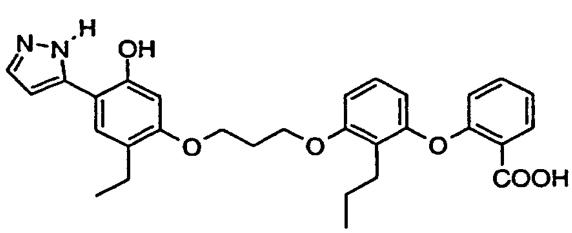

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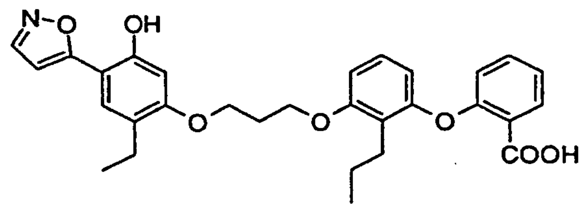
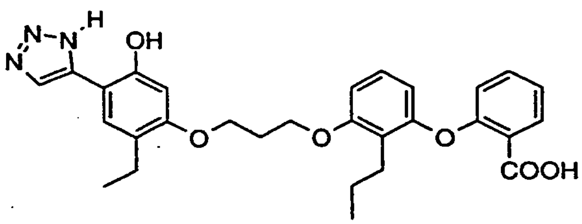
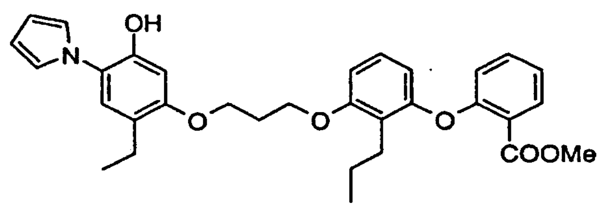

N-O
OH
O
O
O
COOH

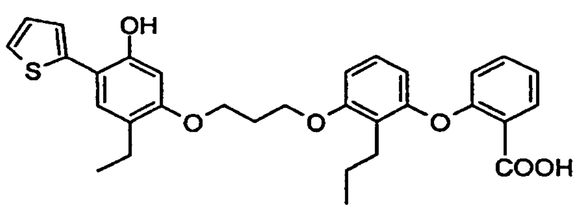
,


N
N-N
H
OH
O
O
O
COOH

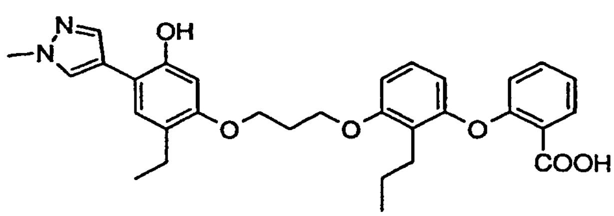
,


N
OH
O
O
O
COOMe

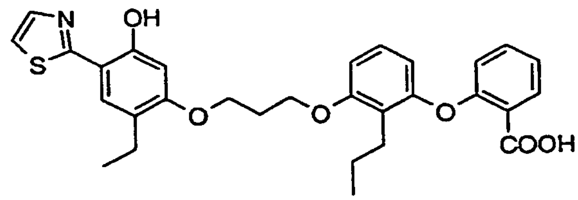
,


S
OH
O
O
O
COOH

,


N
N
OH
O
O
O
COOH

,



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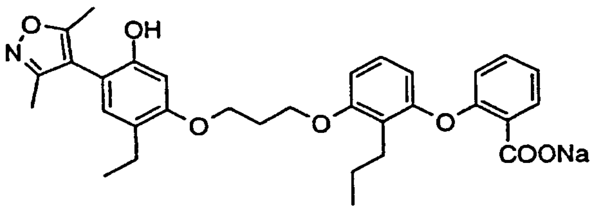

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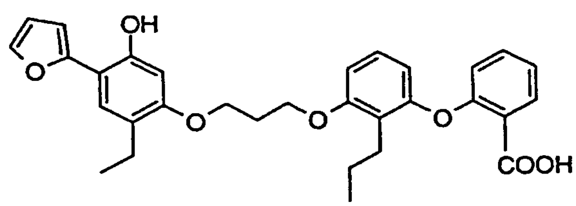

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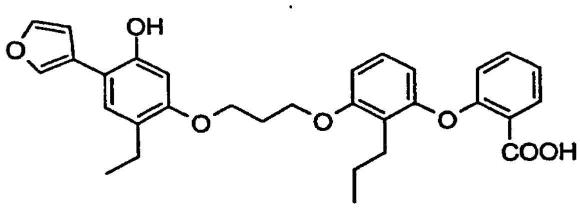

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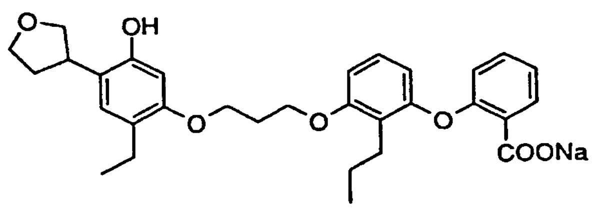

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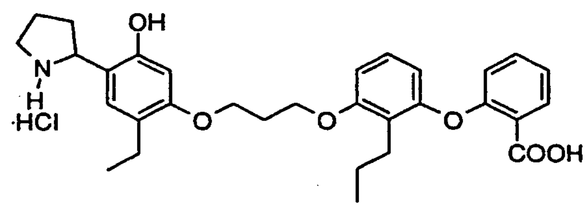

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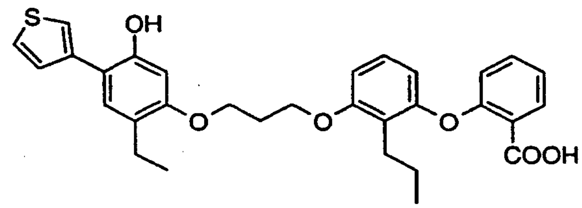

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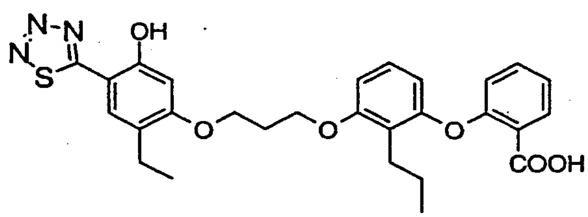

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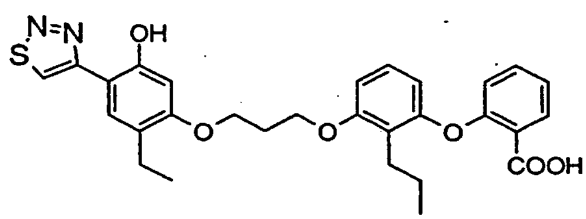

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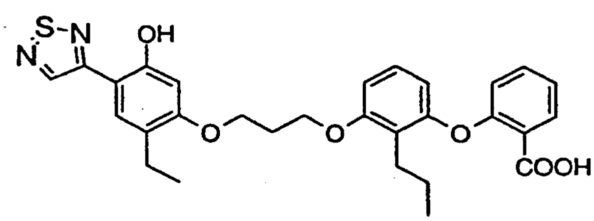

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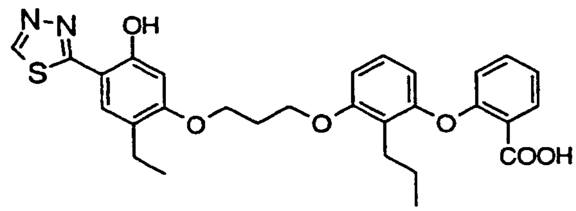

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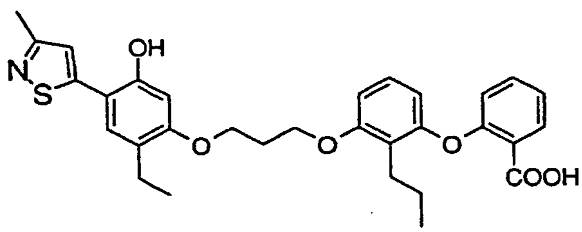

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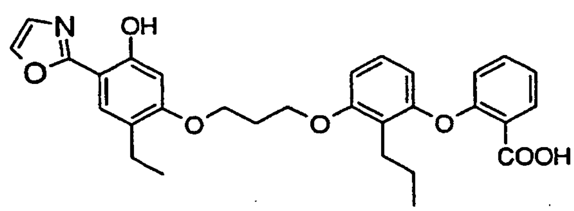
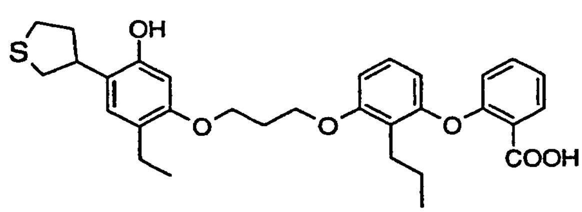


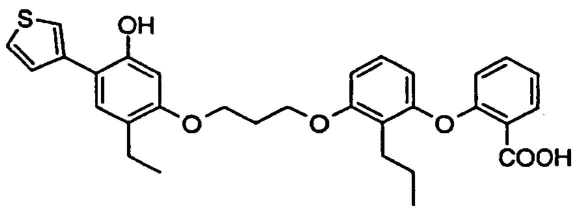
, or



;

or an acid, salt, solvate or prodrug derivative thereof.

21. The method according to claim 20 wherein the leukotriene antagonist is a compound selected from the following:



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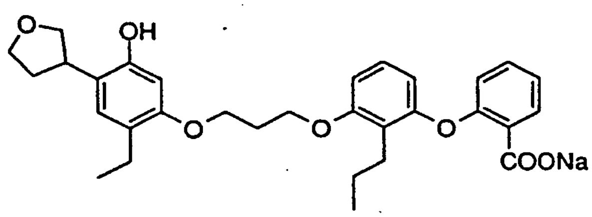

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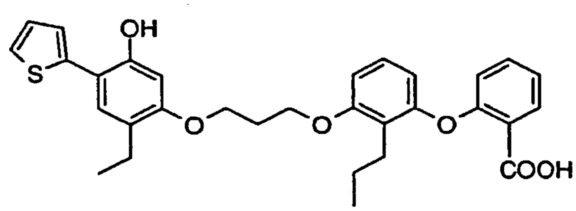

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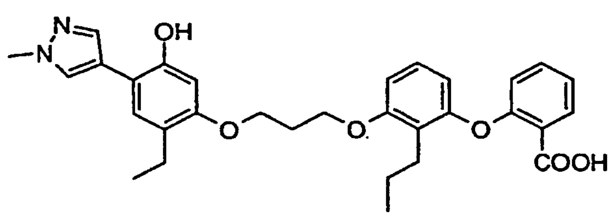

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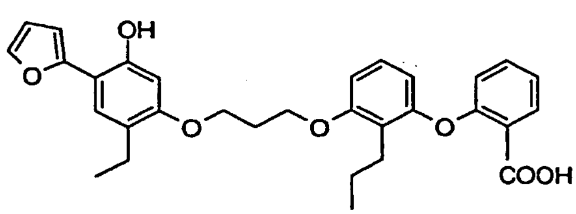

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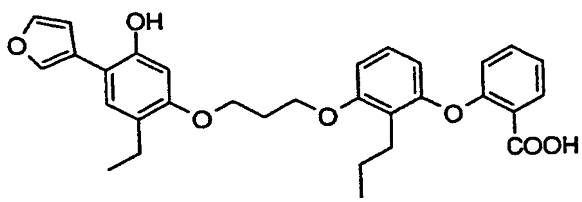
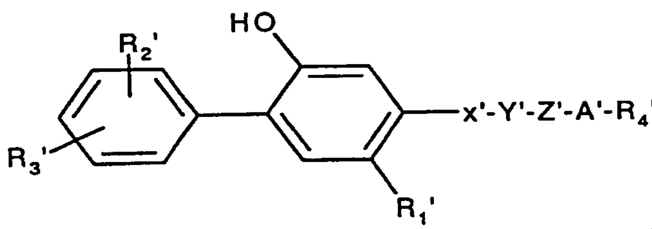


;

or an acid, salt, solvate or prodrug derivative thereof.

22. The method of claim 15 wherein the leukotriene (LTB4) antagonist is represented by a compound of the structure (Formula A):



1

Formula A

or a pharmaceutically acceptable base addition salt thereof, wherein:

R_1' is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2' and R_3' are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-(O)$_q$ S-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X' is -O-, -S-, -C(=O), or -CH_2-;

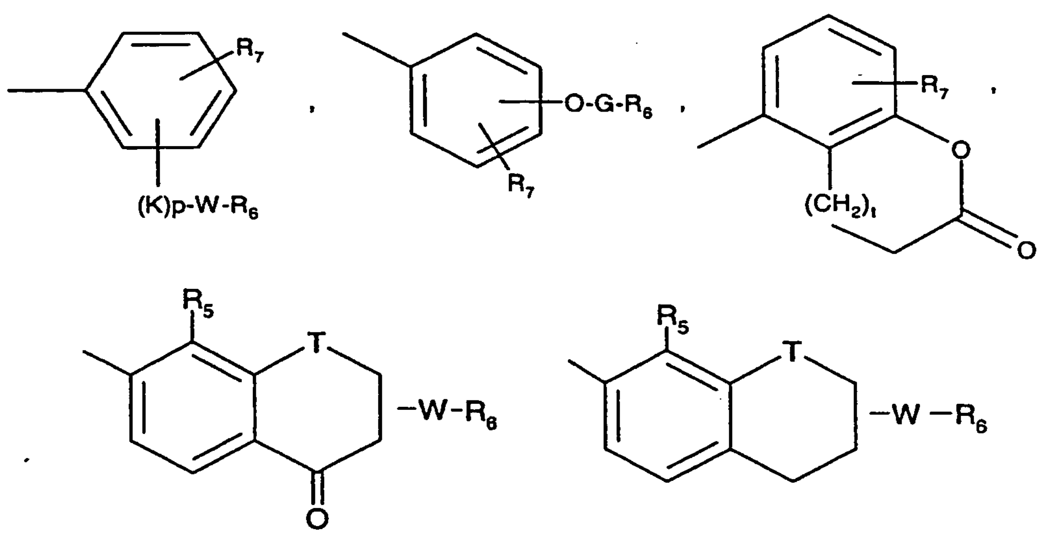
Y' is -O- or -CH_2-;

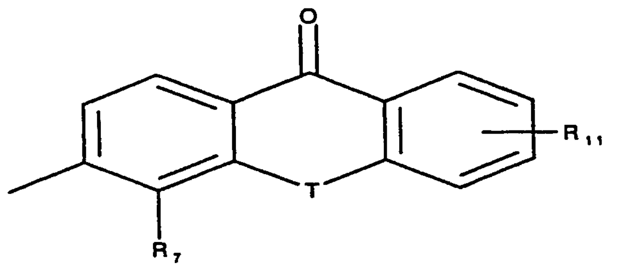
or when taken together, -X'-Y'- is -CH=CH- or -C/C-;

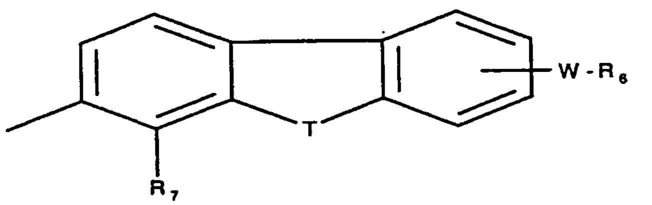
Z′ is a straight or branched chain C_1-C_{10} alkylidenyl;

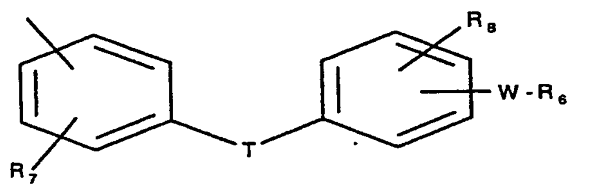
A′ is a bond, -O-, -S-, -CH=CH-, or -CR_aR_b-, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

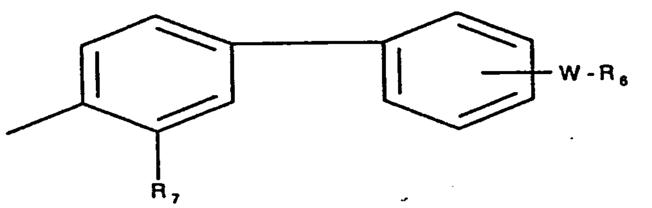
$R_{4'}$ is R_6, or represented by one of the following formulae;











wherein:

each R_6 is independently -COOH, 5-tetrazolyl, -CON$(R_9)_2$, or -CONHSO$_2R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, -W-R_6, -T-G-R_6, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, $-W-R_6$, or $-T-G-R_6$;

each W is a bond or a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $(O)_q$ S-;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

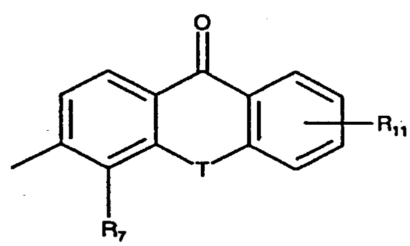
t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

provided when A is -O- or -S-, R_4 is not R_6;

and provided W is not a bond when p is 0.

23. The method according to claim 22 wherein R4'is selected from the following formulae:



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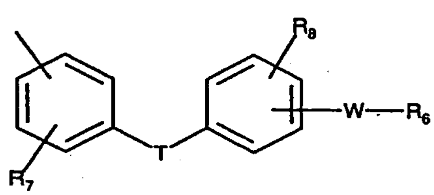
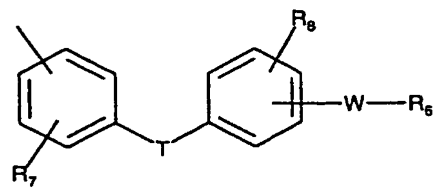


24. The method according to claim 23 wherein R4'is:



25. The method according to claim 24 wherein said compound is selected from the group (A) to (KKKK) consisting of:

A) 2-Methyl-2-(1H-tetrazol-5-yl)-7-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)heptane;

B) 2-Methyl-2-(1H-tetrazol-5-yl)-7-(2-ethyl-4-(3-fluorophenyl)-5-hydroxyphenoxy)heptane;

C) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-dimethylaminocarbonylbutyloxy)phenyl) propionic acid;

D) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

E) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxybutyloxy)phenyl)propionic acid;

F) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-methoxyphenyl)propionic acid;

G) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-(1H-tetrazol-5-yl)butyloxy)phenyl)propionic acid;

H) Methyl 3-(2-(4-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)-(1-butenyl))phenyl)propionate;

I) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)-(1-butenyl))phenyl)propionic acid;

J) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyl)phenyl)propionic acid;

K) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyl)-6-methoxyphenyl)propionic acid;

L) Methyl 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-hydroxyphenyl)propionate;

M) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-hydroxyphenyl)propionic acid;

N) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-butyloxy)phenyl)propionic acid;

O) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-methylthiobutyloxy)phenyl)propionic acid;

P) 3-(2-(3-(2,4-Di-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxybutoxy)phenyl)propionic acid;

Q) 6-Methyl-6-(1H-tetrazol-5-yl)-11-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)undecane;

R) N,N-Dimethyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

S) N-Methanesulfonyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

T) N-Phenylsulfonyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionamide;

U) 3-(2-(3-(2-Butyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

V) Ethyl 3-(2-(4-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyloxy)phenyl)propionate;

W) 3-(2-(4-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)butyloxy)phenyl)propionic acid;

X) Methyl 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-(methoxycarbonyl)phenoxy)phenyl)propionate;

Y) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propionic acid;

Z) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-4-(4-carboxyphenoxy)phenyl)propionic acid;

AA) 3,3-Dimethyl-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

BB) 2-Methyl-2-(1H-tetrazol-5-yl)-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propane;

CC) 2-Methyl-2-(1H-tetrazol-5-yl)-3-hydroxy-3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propane;

DD) 3-(2-(3-(2-Bromo-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

EE) 3-(2-(3-(2-Ethylthio-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionic acid;

FF) Methyl 3-(2-hydroxy-3-(4-methoxycarbonylbutyl)-6-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)propionate;

GG) 5-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-8-(4-carboxybutyl)dihydrocoumarin;

HH) 2-Phenyl-4-ethyl-5-[6-(2H-tetrazol-5-yl)-6-methylheptyloxy]phenol sodium salt;

II) 2-(4-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

JJ) 2-(3-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

KK) 2-(2-Methylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

LL) 2-(4-Methoxyphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

MM) 2-(3-Methoxyphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol sodium salt;

NN) 2-(4-Trifluoromethylphenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

OO) 2-(3-Dimethylaminophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol disodium salt;

PP) 3-(5-(6-(4-Phenyl-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-1,2,3,4 -tetrahydronaphthalen-1(2H)-one)propanoic acid;

QQ) 3-(5-(6-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-

1,2,3,4-tetrahydronaphthalen-1(2H)-one)propanoic acid;

RR) 3-(4-(5-(4-(4-Fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)-2-carboxymethyl-2,3-dihydroinden-1(2H)-one)propanoic acid;

SS) 3,3-Dimethyl-5-(3-(2-carboxyethyl)-4-(3-(4-fluorophenyl)-5-hydroxy-2-ethylphenoxy)propoxy)phenyl)-5-oxopentanoic acid;

TT) 7-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

UU) 8-Propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

VV) 2-[3-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]propanoic acid;

WW) 2-(4-Chlorophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol monosodium salt;

XX) 2-(3,5-Dichlorophenyl)-4-ethyl-5-[6-methyl-6-(2H-tetrazol-5-yl)heptyloxy]phenol monosodium salt;

YY) 3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt;

ZZ) 7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate;

AAA) 2-[2-Propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid sodium salt hemihydrate;

BBB) 3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy][1,1'-biphenyl]-4-propanoic acid disodium salt monohydrate;

CCC) 5-Ethyl-4-[3-[2-propyl-3-[2-(2H-tetrazol-5-yl)phenoxy]phenoxy]propoxy][1,1'-biphenyl]-2-ol disodium salt sesquihydrate;

DDD) 3-[4-[3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9-oxo-9H-xanthene]]propanoic acid sodium salt hemihydrate;

EEE) 2-Fluoro-6-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid disodium salt;

FFF) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt;

GGG) 3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]] propanoic acid disodium salt trihydrate;

HHH) 3-[4-[9-Oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid;

III) 3-[2-[1-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-4-(5-oxo-5-morpholinopentanamido)phenyl]propanoic acid;

JJJ) 2-Fluoro-6-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid disodium salt hydrate;

KKK) 4-Fluoro-2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

LLL) 2-[2-Propyl-3-[5-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]pentoxy]phenoxy]benzoic acid;

MMM) 2-[2-Propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]butoxy]phenoxy]benzoic acid sesquihydrate;

NNN) 2-[2-(2-Methylpropyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

OOO) 2-[2-Butyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid hydrate;

PPP) 2-[2-(Phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid;

QQQ) 2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy] phenylacetic acid;

RRR) 2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid;

SSS) 2-[[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl] benzoic acid;

TTT) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid;

UUU) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfinyl] benzoic acid;

VVV) 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfonyl] benzoic acid hydrate;

WWW) 5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-

hydroxyphenoxy]propoxy]phenyl]-4-pentynoic acid disodium salt 0.4 hydrate;

XXX) 1-Phenyl-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

YYY) 1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

ZZZ) 1-(4-(Dimethylaminocarbonylmethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

AAAA) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)-E-propenoic acid;

BBBB) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)-2-methyl-E-propenoic acid;

CCCC) 5-(2-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)phenyl)ethyl)-1H-tetrazole;

DDDD) 3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-4-(4-carboxybutyloxy)phenyl)propionic acid;

EEEE) 5-[3-[4-(4-Fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-one;

FFFF) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}phenyl)propanoic acid;

GGGG) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-4-propylphenyl)propanoic acid sodium salt;

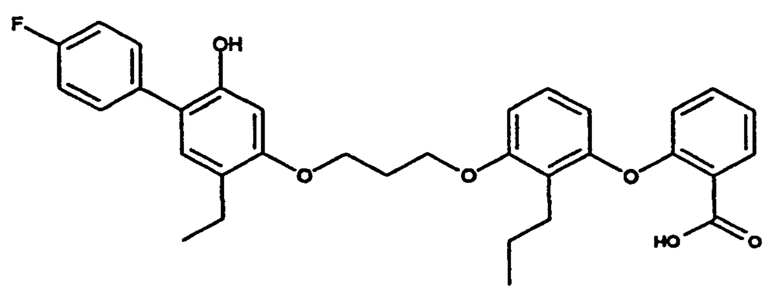
HHHH) 3-(4-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-3-propylphenyl)propanoic acid;

IIII) 3-(3-{3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenyloxy]propoxy}-2-propylphenyl)propanoic acid;

JJJJ) 3-{3-[3-(2-Ethyl-5-hydroxyphenyloxy)propoxy]-2-propylphenyl}propanoic acid disodium salt; and

KKKK) 2-[3-[3-[2-Ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid disodium salt hemihydrate.

26. The method according to claim 24 wherein the leukotriene (LTB4) antagonist is a compound of the structure (Formula B):



Formula B

namely, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxybenzoic acid, and the pharmaceutically acceptable salts thereof.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34197 A3

(51) International Patent Classification[7]: A61K 41/00

(21) International Application Number: PCT/US00/30839

(22) International Filing Date:
9 November 2000 (09.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/164,704 11 November 1999 (11.11.1999) US

(71) Applicant (*for all designated States except US*): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
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(74) Agents: **SAYLES, Michael, J.** et al.: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/34197 A3

(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: A method of treating cancer with radiation, in conjunction with the administration of a leukotriene (LTB4) antagonist is disclosed.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/30839

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBASE, BIOSIS, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 06604 A (DEUTSCHES KREBSFORSCH ;LEIER INKA (DE); JEDLITSCHKY GABRIELE (DE);) 7 March 1996 (1996-03-07) cited in the application claims & US 5 543 428 A 6 August 1996 (1996-08-06) ---	1-26
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E	WO 01 34137 A (BEIGHT DOUGLAS WADE ;BENJAMIN ROGER STUART (US); MCMILLEN WILLIAM) 17 May 2001 (2001-05-17) claims --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2001	09/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/30839

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 34135 A (BEIGHT DOUGLAS WADE ;MCMILLEN WILLIAM THOMAS (US); TEICHER BEVERLY) 17 May 2001 (2001-05-17) claims	1
Y	EP 0 544 488 A (LILLY CO ELI) 2 June 1993 (1993-06-02) claims	1-26

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-26 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds cited in the examples and the closely related compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/30839

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